FIRST ANNUAL REPORT OF THE DIRECTOR, ONAL INSTITUTE OF ARTHRITIS, DIABETES, AND DIGESTIVE AND KIDNEY DISEASES

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health

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NATIONAL
INSTITUTE OF
ARTHRITIS,
DIABETES, &
DIGESTIVE &
KIDNEY DISEASES

National Institutes of Health
Bethesda, Maryland 20205

This Report is the first of its kind for NIADDK. It was mandated by P.L. 96-538, now section 434(e) of the Public Health Service Act. We hope you enjoy perusing it.

Lester B. Salans, M.D.
Director, NIADDK

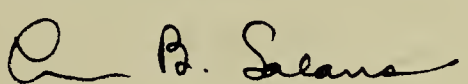
FOREWORD

It is our footsteps behind that often mark the path ahead in science and medicine. In the 30-year journey, to date, of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK), these footsteps are many and deep—evidence of bold advances against a menacing array of chronic, disabling, and life-threatening disorders. These advances have been made through an aggressive attack by NIADDK scientists in the intramural laboratories of the National Institutes of Health as well as by NIADDK-supported investigators in hospitals, universities, and research centers throughout the United States. A primary purpose of this report is to chronicle these research accomplishments and their contributions to improved health care.

Matching the past three decades of impressive progress is the challenge of the future. The magnitude and severity of the health problems confronting NIADDK are immense, as is the urgency of the efforts necessary to reduce their toll of premature death, disability, and human suffering. Because the underlying causes of many of these diseases remain unknown, the Institute is committed above all to an intensive program of basic and clinical research aimed at elucidating the nature and mechanisms of the disease process. Another important purpose of this report, therefore, is to describe the activities under way and planned by the Institute to narrow the gaps in our current state of knowledge in arthritis, diabetes, digestive and kidney diseases, and related disorders.

From origins that can be traced to some of the oldest laboratories in the Public Health Service, NIADDK enters the 1980s with an unmistakable sense of excitement. Acting in concert with NIADDK advisory groups, national commissions, and various task forces, and through Congress's enactment of special legislation concerning arthritis, diabetes, and digestive and kidney diseases, the Institute has greatly expanded its responsibilities, resulting in ambitious plans of action which have begun to be implemented in recent years. These initiatives, based on continuing basic and applied research efforts, are expected to yield significant gains toward the prevention, cure, or long-term control of diseases affecting virtually every citizen in the Nation.

This report was developed in response to the most recent legislation affecting NIADDK. Public Law 96-538, signed on December 17, 1980, changed the name of the Institute—from National Institute of Arthritis, Metabolism, and Digestive Diseases to National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases—and formalized several other changes which have taken place in the Institute's programs and organization. One requirement of the new law is the issuance of an annual report by the Director, to the President and the Congress, describing the Institute's activities. This report is intended to fulfill that requirement comprehensively and lucidly, to convey the spirit of challenge and achievement, to take an appreciative glance behind and a hopeful look ahead.



Lester B. Salans, M.D.
Director
National Institute of Arthritis, Diabetes,
and Digestive and Kidney Diseases

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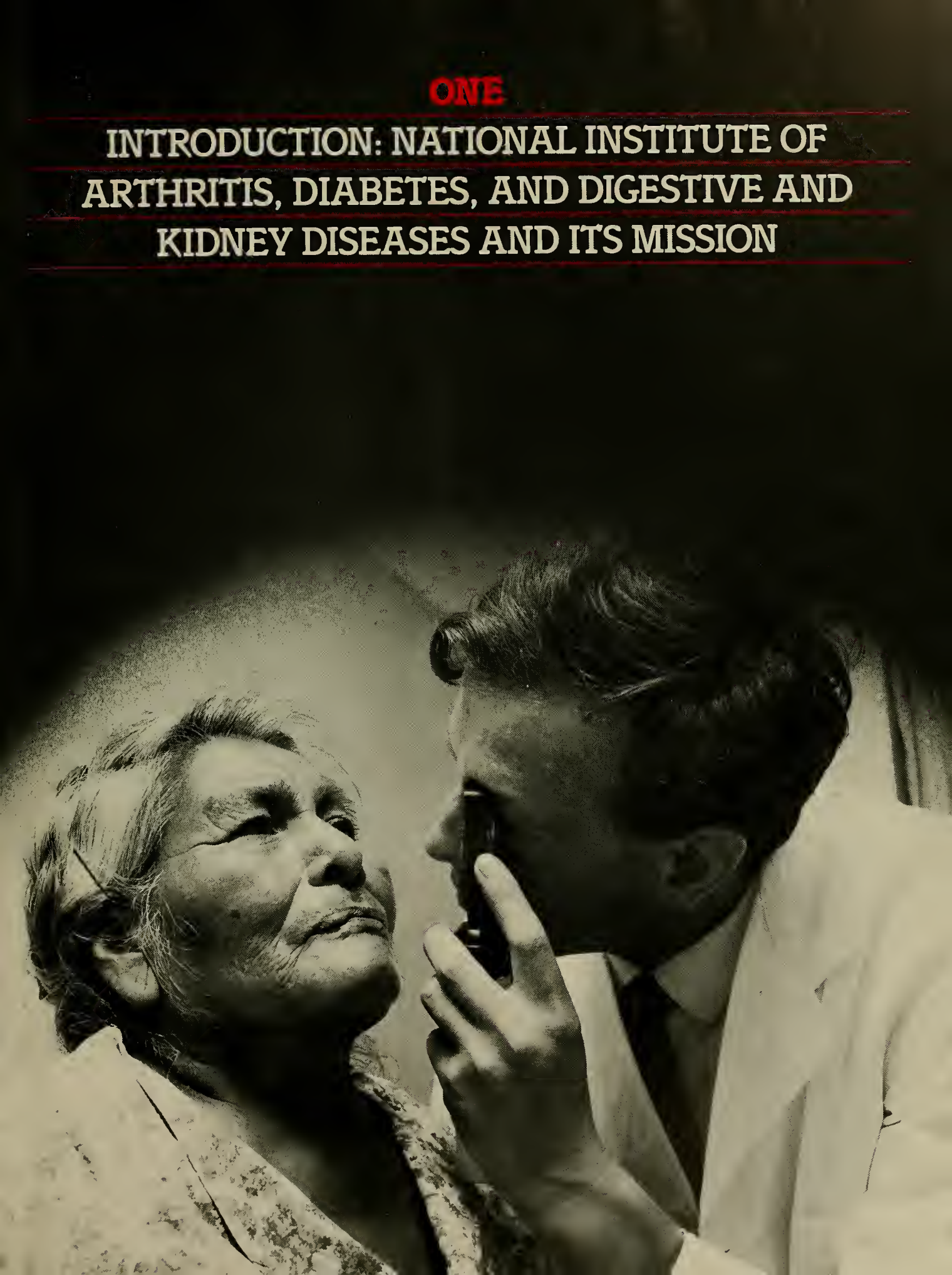

Photographs:

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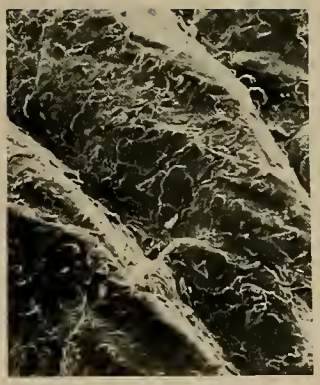


INTRODUCTION: NATIONAL INSTITUTE OF ARTHRITIS, DIABETES, AND DIGESTIVE AND KIDNEY DISEASES AND ITS MISSION

The development of knowledge about diseases is a critical step toward their control. Since 1950, the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) has been seeking answers to the many puzzling questions about disease processes and the effects of these destructive forces on body organs and systems. The contributions of NIADDK's research programs and activities have been integral to the enormous expansion of biomedical knowledge generated by the National Institutes of Health (NIH) in the past three decades.

NIADDK is 1 of 11 Institutes that compose the National Institutes of Health. From its modest beginnings in 1887 as the one-room Laboratory of Hygiene, NIH has grown to become a major agency in the Department of Health and Human Services (DHHS) and is the largest and most successful biomedical research organization in the world. Situated on 306 acres of land in Bethesda, Maryland, NIH incorporates hundreds of sophisticated research laboratories, clinical care facilities, administrative office buildings, and a national medical library. It is from this unique community of research scientists, clinicians, health care professionals, and health program planners and administrators that much of the Nation's biomedical research effort is directed.

Over the years, the programs and activities sponsored or conducted by NIH have expanded substantially as the demand for knowledge about life-threatening and disabling diseases has grown. To accommodate this demand and facilitate progress toward carrying out the mission of NIH, each of the 11 NIH Institutes has taken responsibility for fostering research in one or several related disease areas or health problems. The Institutes function as administrative units within which research activities are planned and coordinated for conduct at the NIH complex or funded for execution at research facilities, academic institutions, and health facilities across the country and abroad.

Within NIH, NIADDK's emphasis on research into the causes of a vast array of chronic and disabling diseases has earned it recognition as an Institute whose basic research responsibilities are attuned to the needs of other NIH Institutes as well, and whose accomplishments have a far-reaching impact in disease areas outside its own purview.

The traditional and continued focus on basic research that has guided NIADDK's research program has evolved from the realization that a basic understanding of the intrinsic nature of each disease is imperative. Thus, the Institute has an important stake in the pursuit of research using the fundamental sciences, such as biochemistry, biology, physics, chemistry, pathology, genetics, immunology, physiology, and pharmacology, which provide the foundation of knowledge pertinent to diseases that can affect many organs or organ systems in the body, namely the various arthritic, muscular, connective tissue, and skin disorders; diabetes and other abnormalities of the endocrine system as well as metabolic disturbances; diseases of the gastrointestinal

tract and nutritional disorders; and kidney and blood diseases.

Although the successes achieved through NIADDK's research programs are impressive, such progress must be meaningfully applied to improvement of the Nation's health. It is for that reason that the Institute supports clinical trials and other programs involving technology transfer, and collects, publishes, and disseminates information about current research for scientists, health care professionals, and the public. In addition, NIADDK fosters communication with a number of professional associations and voluntary health organizations in order to enhance its relationship with those directly or indirectly involved in improving the health of the American people.

NIADDK is a multifaceted Institute whose development has been and continues to be responsive to the varied health needs of our Nation. Its programs have the potential of touching the lives of many millions of Americans who are faced each day with the distress associated with chronic, disabling diseases. Finding the answers to the many questions surrounding these diseases and health problems, in the hope that suffering and disability can be alleviated in their economic as well as their personal dimension, has shaped NIADDK's history and continues to guide its efforts in the sphere of biomedical research.

THE ORIGINS OF NIADDK

With the end of World War II, in the late 1940s government concern turned inward to look at Federal programs and policies that had been allowed to languish and stagnate during the war years, and the Nation's biomedical research program moved to the forefront of domestic policy issues. The National Institutes of Health was part of the resultant growth and expansion in government activities as public demands for more and better health services required a renewed emphasis on the detection, treatment, control, and cure of diseases and health problems that continued to undermine the well-being of the American people.

Although new research components were added to the NIH complex to accommodate the agency's increased responsibilities, no Institute had as its primary mission the promotion of research investigations into the cause, treatment, or potential cure of the chronic, disabling diseases now addressed by NIADDK. Millions of Americans were suffering with these disorders, obtaining little or no relief in the form of effective prevention, therapies, or cure. Moreover, it soon became apparent that any long-range effort directed at the conquest of such diseases must evolve from a sound foundation of basic science knowledge and understanding.

Clearly, the establishment of a federally supported organization focusing its investigative efforts on fundamental biomedical research in addition to clinical research in chronic disease was long overdue. Concerned scientists, health care providers, and the public convinced Congress that such an Institute would be an asset for the research programs being conducted or sponsored by the NIH. Consequently, Congress approved the Omnibus Medical Research Act, authorizing the establishment of the National Institute of Arthritis and Metabolic Diseases (NIAMD, incorporating the existing Experimental Biology and Medicine Institute) within the Public Health Service. On August 15, 1950, President Truman signed the act into law (P.L. 81-629), thereby initiating NIAMD as a component of the National Institutes of Health.

30 YEARS OF PROGRESS AND GROWTH

With the establishment of NIAMD in 1950, a new area of important biomedical research needs was addressed. The mandate given to the new Institute, namely to

> " ... conduct researches relating to the cause, prevention, and methods of diagnosis and treatment of arthritis and rheumatism and other metabolic diseases, to assist and foster such researches and other activities by public and private agencies, and promote the coordination of all such researches, and to provide training in matters relating to such diseases ... ,"

gave priority and impetus to research in areas that previously had been largely unexplored.

The range of Institute research programs was broadened as new areas of research interest were added to existing responsibilities, but the emphasis on basic research remained and continues to provide the focus and direction for investigations sponsored and conducted by the Institute today. Figure 1 shows the significant events in NIADDK's history that have contributed to the growth of the Institute and the increasing breadth and depth of its research responsibilities.

During its first decade, NIAMD greatly expanded its programs and operations to accommodate the growing list of diseases and health problems that came under its research umbrella. Between 1950 and 1960 a number of notable events helped to guide the Institute's development:

1950

- The **National Institute of Arthritis and Metabolic Diseases** was established pursuant to the provisions of P.L. 81-692, the Omnibus Medical Research Act.

- The **National Advisory Arthritis and Metabolic Diseases Council** was formed and held its first meeting to approve the Institute's first grants.

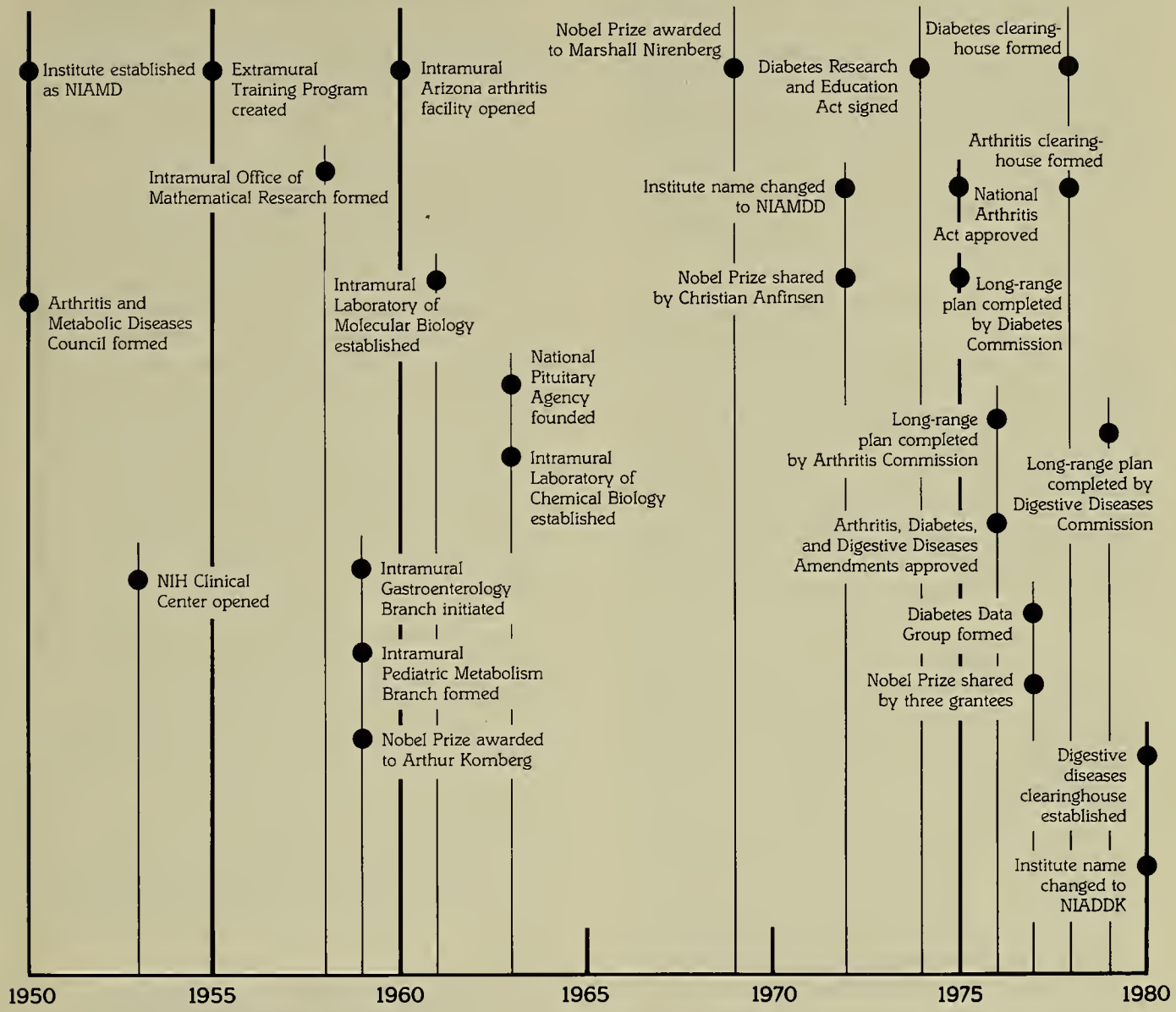
1953

- On July 2 the **NIH Clinical Center** (research hospital) opened, broadening the scope of NIAMD intramural activities to include intensive research studies with patients.

1955

- The **Extramural Training Program** was established.

Figure 1.—Significant events in the history of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases



1959

■ **Dr. Arthur Kornberg,** former chief of the Institute's Enzyme and Metabolism Section, won the Nobel Prize for the first successful synthesis of nucleic acids—components of DNA, the determinants of inheritance.

As the Institute moved into its second decade, increasing activity in basic biomedical research and emerging research opportunities continued to redefine, expand, and intensify its programs in a broad range of areas. Major events in this development stage included the following:

1960

■ An important epidemiological study of osteoarthritis and rheumatoid arthritis among Blackfoot and Pima Indians in Montana and Arizona led to the establishment of permanent facilities in Phoenix, Arizona, for both epidemiological and clinical studies of **Southwestern Indian populations.**

1963

■ The **National Pituitary Agency** was established to increase the availability of human growth hormone for use in clinical growth research programs.

1969

■ The Nobel Prize was awarded to **Dr. Marshall W. Nirenberg,** then of the National Heart Institute, for his success in partially cracking the genetic code, an achievement that he reported during his earlier association with NIAMD.

The Institute embarked on its third decade with a new name—the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD)—and a renewed commitment to understand the etiology and natural history and improve the diagnosis and treatment of the chronic and disabling diseases within its purview. The challenge to design a workable framework through which research in a growing number of disease areas could be efficiently administered was met through the development of four separate "clusters" of research activity:

- Arthritis, musculoskeletal, and skin diseases;
- Diabetes, endocrinology, and metabolic diseases;
- Digestive diseases and nutrition; and
- Kidney, urologic, and blood diseases.

The "cluster" concept, which is still in use, provided for individual emphasis as appropriate for each grouping of health problems, while fostering the coordination of efforts in areas that are closely related or overlapping. The progress in basic research during the previous two decades had provided the base of knowledge from which intensive research into the causes and treatment of chronic diseases would emanate in the 1970s, further enhancing NIAMDD's role as a cornerstone of basic science in the NIH community. Among the significant events in this active period of NIAMDD's history were:

1972

- Public Law 92-305 focused attention on research in digestive diseases by changing the name of the Institute to the **National Institute of Arthritis, Metabolism, and Digestive Diseases** and by designating a Digestive Diseases Committee within the Institute's National Advisory Council.
- **Dr. Christian B. Anfinsen,** chief of the Institute's Laboratory of Chemical Biology, shared a Nobel Prize with two other American scientists for his demonstration of one of the most important simplifying concepts of molecular biology—that the three-dimensional conformation of a native protein is determined by the chemistry of its amino acid sequence—work that contributed to knowledge concerning the mechanisms of metabolic disorders.

1974

- Public Law 93-354, the **National Diabetes Mellitus Research and Education Act,** was signed, authorizing centers for research and training in diabetes and establishment of an intergovernmental diabetes coordinating committee, including NIAMDD and six other NIH Institutes.

1975

- The **National Arthritis Act** (P.L. 93-640) provided for establishment of the **National Commission on Arthritis and Related Musculoskeletal Diseases,** centers for research and training in arthritis and rheumatic diseases, and a data bank. The act also called for an overall plan aimed at the investigation of the epidemiology, etiology, control, and prevention of these disorders.
- The **National Commission on Diabetes** completed its report, the **Long-Range Plan to Combat Diabetes,** which recommended expansion and coordination of programs in diabetes and related research; the creation of a program of diabetes centers; acceleration of efforts in health care, education, and control programs; and the establishment of a national diabetes advisory board.

1976

- The **National Commission on Arthritis and Related Musculoskeletal Diseases** delivered to Congress the **Arthritis Plan,** which recommended the creation of a national network of multipurpose arthritis centers, a series of epidemiological studies on arthritis, and the development of an arthritis data system, a national arthritis information clearinghouse, and a national arthritis advisory board.
- Public Law 94-562, the **Arthritis, Diabetes, and Digestive Diseases Amendments of 1976,** provided for establishment of the National Arthritis Advisory Board and National Diabetes Advisory Board to advise the Institute on research, training, prevention, and control programs directed toward eradication of diseases and health problems within their respective areas of interest. The amendments also established the **National Commission on Digestive Diseases.**

1977

- Three scientists won the Nobel Prize for research supported in part by NIAMDD. **Drs. Roger C. L. Guillemin and Andrew V. Schally** shared the award, for their discoveries involving peptide hormone production of the brain, with **Dr. Rosalyn S. Yalow,** for her work in the development of radioimmunoassays of peptide hormones.

1978

- The **National Diabetes Information Clearinghouse** was formally established as the central point for the collection and dissemination of information on sources of diabetes information and educational materials.
- The **Arthritis Information Clearinghouse** was organized to collect, store, and distribute information about materials and programs addressing arthritis and related diseases.

1979

- The **National Commission on Digestive Diseases** submitted to Congress its **National Long-Range Plan to Combat Digestive Diseases,** which recommended the establishment of a national digestive diseases advisory board, an information clearinghouse, and increased emphasis on medical school programs in digestive diseases.

1980

- The **National Digestive Diseases Education and Information Clearinghouse** was established to identify, collect, analyze, and disseminate information about digestive diseases and to serve as a

national education resource for patients, their families, physicians, and other health professionals.

- Enactment of P.L. 96-538, the **Health Programs Extension Act,** authorized a change in the Institute's name to the **National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases;** Institute associate directors for each of the four research clusters; and Advisory Council subcommittees for each cluster.

For each of the three national commissions described above, Congress mandated a group with well-delineated composition and charged it with developing a national plan to combat a major health problem. Each of the commissions was composed of experts in the particular disease area and of civic leaders and laymen with a strong interest in that disease or health problem. In each case, the Institute Director and the associate director for the disease program involved were ex officio members of the commission and participated actively in its deliberations and activities.

Each of the commissions was specifically mandated to review and assess the state of the science in its area of interest and devise a national plan to strengthen and advance research in that area. The activities of the commissions were also aimed at improving and expanding health care as well as public and professional education concerning the disease. Once these plans were completed and presented to Congress, the commissions were disbanded.

With the advent of the 1980s, NIADDK looks forward to a decade offering numerous opportunities for continued research into the fundamental aspects of disease as well as the enhancement of programs and activities aimed at treatment, prevention, and control. With the guidelines provided by the national commissions, the Institute will continue to pursue investigations of arthritis, diabetes, digestive and kidney diseases, and related disorders in the hope of even greater progress toward eradicating these diseases.

RESEARCH ON CHRONIC DISEASE: THE MISSION OF NIADDK

The programs of NIADDK are of profound importance to the American people, dealing with a wide range of basic and clinical science investigations in a wide range of categorical diseases (many of which are listed in table 1). There is virtually no population group in this country that is immune to attack by one or more of the diseases or disorders within NIADDK's purview. The impact of these diseases can be seen in table 2, which shows the prevalence, or number of affected individuals in the United States, and the approximate economic costs to the American public of some of the major diseases. These economic estimates account for only those costs associated with care, treatment, and productivity lost because of absenteeism from work. The more profound costs, in terms of human suffering, cannot easily be measured, but they are no less significant. Finding effective methods to prevent, control, and treat these diseases and disorders, through its various research programs and activities, is the mission of NIADDK.

Because of the number of diseases and disorders within each program area, and the challenge of diversity that they entail, NIADDK has continued active support of basic science relevant to disease research. It is only through understanding of basic intrinsic factors in the development and progression of chronic disease that effective interventions or treatments will be forthcoming.

ARTHRITIS, MUSCULOSKELETAL, AND SKIN DISEASES

The research being supported and conducted within the arthritis, musculoskeletal, and skin diseases cluster focuses on diseases and disorders including the various types of arthritis, diseases of skeletal support structures, and diseases of the skin. Although such health problems are generally not fatal, they cause pain and widespread disability. Depending on the extent of disease progression, they can be partially controlled through medication and/or other types of therapy. Nevertheless, the costs associated with the diseases and health problems within this cluster are tremendous. Many millions of Americans suffer the effects of these disorders at a total estimated cost ranging from $13 billion to $17 billion each year for medical care and lost productivity.

High priority for research in this area is given to the study of arthritis and related afflictions. Arthritis, a term that includes over 100 disorders, is the most common crippling disability as well as mankind's oldest known chronic illness. Over 31 million Americans suffer from arthritis and related disorders such as systemic lupus erythematosus, gout, and other diseases with symptoms ranging from mild discomfort to severe pain and total disability.

The musculoskeletal diseases program supports research directed toward an understanding of the structure and function of the bones, joints, and skeletal support structures.

The skin diseases program supports clinical and laboratory research of both normal and diseased skin to obtain a better understanding of the causes and processes of various skin diseases.

Because this cluster encompasses a wide range of diseases and health problems, research aimed at developing effective medications and treatments necessarily involves an equally diverse number of scientific disciplines and technologies. For example, the development and design of prosthetic devices for bone, joint, and hip replacements require knowledge of kinetics, biomechanics, and engineering—technologies that have only recently moved to the forefront of biomedical research. Moreover, basic science disciplines are used to study immunological factors, infectious agents, genetic factors, and structure and function to provide the foundation

Table 1.—NIADDK research areas: some representative examples

ARTHRITIS, MUSCULOSKELETAL, AND SKIN DISEASES PROGRAM

Arthritis and Related Disorders	Musculoskeletal Diseases	Skin Diseases
Rheumatoid arthritis	Paget's disease	Psoriasis
Osteoarthritis	Osteoporosis	Acne
Juvenile arthritis	Osteopetrosis	Bullous diseases
Systemic lupus erythematosus	Osteogenesis imperfecta	Ichthyosis
Gout	Bone metabolism	Vitiligo
Lyme arthritis	Bone fractures and healing	Eczematous and immunologic diseases
Epidemic polyarthritis	Artificial joints and biomaterials	Allergic dermatoses
Psoriatic arthritis	Congenital and acquired skeletal anomalies	Cutis laxa
Inherited connective tissue diseases	Low back pain	Photobiology
Systemic sclerosis (scleroderma)	Exercise pathophysiology	Heritable skin disorders
Spondyloarthropathies		
Muscle structure and function		
Muscle pathophysiology		

DIABETES, ENDOCRINOLOGY, AND METABOLIC DISEASES PROGRAM

Diabetes	Endocrine Diseases	Metabolic Diseases
Insulin-dependent diabetes	Disorders of endocrine glands (thyroid, pituitary, etc.)	Inborn errors of metabolism
Noninsulin-dependent diabetes	Hormone synthesis, secretion, action, and interactions	Animal models of inbom metabolic errors
Complications of diabetes	Hormonal imbalances	Cystic fibrosis
Etiologic factors in diabetes	Research availability of hormones	Enzyme structure and function
Immunology and diabetes	Growth factors	Cellular oxidation and biological membranes
Insulin receptors	Recombinant DNA production of peptide hormones	Cell surface receptors
Insulin resistance	Calcium and body function	Reye's syndrome
Insulin delivery devices	Neuroendocrinology and brain peptides	Noninvasive instrumentation in metabolic research
Pancreatic islet cell transplantation	Hormones and pharmacotherapy	
Nutrition and diabetes		
Animal models of diabetes		

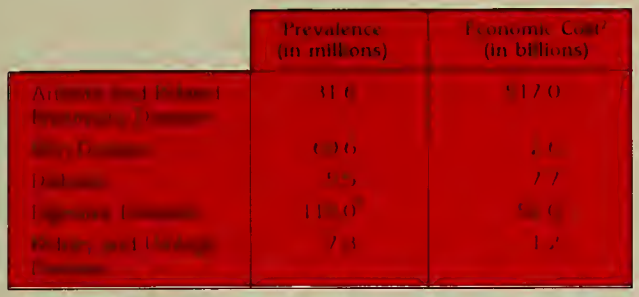
DIGESTIVE DISEASES AND NUTRITION PROGRAM

Esophageal, Gastric, and Colonic Diseases	Intestinal and Pancreatic Diseases	Liver and Biliary Tract Diseases	Nutrition
Ulcer disease	Gastrointestinal hormones	Hepatitis	Nutritional requirements in health and disease
Functional bowel disorders	Small intestine structure and function	Cirrhosis	Obesity
Gastrointestinal motility dysfunctions	Intestinal absorption	Genetic liver disease	Regulation of fuel mobilization and storage
Inflammatory bowel diseases	Malabsorption syndromes	Hepatic transport defects	Exercise and energy metabolism
Gastrointestinal bleeding	Diarrheal diseases	Gallstones	Nutritional needs in disease
Endoscopy in research, diagnosis, and treatment	Pancreatitis	Cholesterol and bile acid metabolism	Nutritional status assessment
Gastrointestinal growth and regeneration	Pancreas transplantation	Liver regeneration	Dietary fiber
Structure, function, and disease of the esophagus and stomach	Salivary gland structure, function, metabolism, and secretion	Liver transplantation	Essential trace elements and minerals
			Nutrient transport, utilization, and function
			Special supportive nutrition in disease

KIDNEY, UROLOGIC, AND BLOOD DISEASES PROGRAM

Renal Physiology and Pathophysiology	Urologic Diseases	Chronic Renal Diseases	Blood Diseases
Renal metabolism and transport	Nephrolithiasis and urolithiasis	End-stage renal disease	Anemias of genetic origin
Renin and hemodynamics	Congenital anomalies of the urinary tract	Dialysis therapy	Nutritional anemias
Hypothalamic regulation of water balance	Bladder dysfunction	Renal dialysis and its complications	Metabolic disorders of iron transport and storage
Immunologic basis of renal disease	Vesicoureteral reflux	Kidney transplantation	Disorders of blood cell production
Glomerulonephritis	Urinary tract infection	Nutrition and chronic renal disease	Hematopoietic tissue transplantation immunology
Interstitial nephritis	Prostatic hypertrophy		Autoimmune hematologic diseases
Acute renal failure	Prostatitis		Iron chelation therapy

Table 2.—Prevalence and economic costs of selected disease groups[1]



	Prevalence (in millions)	Economic Cost[2] (in billions)
[illegible]	31.6	$170
[illegible]	0.6	2.6
[illegible]	5.5	7.7
[illegible]	11.0	5.6
[illegible]	7.3	1.7

[1]Based on 1979 data.

[2]Including direct costs for hospital care, professional services, and drugs as well as indirect costs of productivity lost because of death and disability.

[3]Including malignancies associated with the digestive organs.

for much of the research directed at preventing or controlling these diseases.

DIABETES, ENDOCRINOLOGY, AND METABOLIC DISEASES

The human body is composed of a complex, interrelated network of organs that rely, to a certain degree, on products from other components of the body to function normally. An imbalance that affects the production of a substance needed to regulate an organ or system may result, therefore, in far-reaching effects on other related organ systems, to the detriment of vital life processes.

Diabetes mellitus represents one such imbalance. Diabetes is characterized by decreased utilization of glucose by body cells, increased mobilization of fats from fat storage areas, and diminished deposition of protein in the tissues of the body, most often because of a deficiency in insulin production or impairment of insulin function. Clearly, diabetes has numerous detrimental effects on body systems; and, while appropriate management can partially control certain aspects of the disease, complications such as increased risk of heart, kidney, and blood vessel disease, nervous system impairment, and blindness are a serious threat. These complications are the major source of morbidity and mortality associated with the disease and seriously impair the patient's quality of life in addition to increasing the risk of premature death. Roughly 5.5 million people in this country have been diagnosed as diabetic, and it is estimated that another 5 million have abnormalities of glucose tolerance that have thus far escaped detection but will emerge later in life—clear indications that diabetes is a serious, widespread health problem.

Diabetes continues to be one of the most important areas of research supported by NIADDK. Research studies are being pursued from a variety of perspectives—from basic investigations of insulin synthesis, storage, and release to the use of sophisticated computerized technology and epidemiologic research—and involve investigators from many disciplines. The long-range objective of NIADDK-supported research in diabetes is to elucidate the means by which the disease and its potentially life-threatening complications can be prevented, better controlled, or cured.

In addition to diabetes research, investigations of other endocrinological diseases and disorders are also supported by this program cluster. These include studies on thyroid, pituitary, and adrenal disorders; neuroendocrinology; the mechanism of action of hormones; the relationship of calcium to normal body function; the prostaglandins; cell receptors; and the development, structure, and metabolism of endocrine glands.

Since the effects of hormones are manifested through metabolic events within the cell, and because the endocrine system exerts the main regulatory influence on overall metabolism, the disciplines of endocrinology and metabolism have become intertwined, and with them the field of genetically determined metabolic diseases. NIADDK's mission through its metabolic diseases program is to acquire an understanding of the etiology, pathogenesis, and treatment of acquired or inborn errors of metabolism through support of research into enzymatic mechanisms and their regulation, biological transport, and membrane structure. This support is evidenced by NIADDK's long-standing commitment to the study of cystic fibrosis as well as other metabolic disorders.

DIGESTIVE DISEASES AND NUTRITION

Disorders of the digestive system affect the organs that contribute to the processing of the nutrients needed to sustain bodily functions. Consequently, normal function and diseases that disrupt the intestines, esophagus, salivary glands, pancreas, liver, stomach, and gallbladder, as well as nutritional disorders, are the major focus of research within this area.

More than 20 million Americans are afflicted with diseases of the digestive system. These disorders exact a high toll in terms of suffering and economic costs. They are disabling, often chronic in nature, and are responsible for $52 billion in losses to the Nation's economy each year. But the greater cost in terms of lives lost is staggering—approximately 200,000 deaths each year (including those associated with malignancies). Included among the digestive diseases are gallstones, ulcer disease, gastrointestinal hemorrhage, hepatic cirrhosis, hepatitis, ulcerative colitis and Crohn's disease, and pancreatitis.

NIADDK's mission with respect to digestive diseases is twofold—to reduce the suffering associated with these diseases and to reduce their economic impact. In carrying out its mission, NIADDK's program in digestive diseases supports basic scientific investigations of the structure, function, and diseases of the digestive system organs as well as clinical studies to develop and evaluate new pharmacological agents and noninvasive diagnostic and therapeutic methods for the clinical management of these diseases.

In addition to the high toll taken by digestive diseases, diet alone is believed to play a significant role in 6 out of 10 of the Nation's leading causes of death, including heart disease, stroke, cancer, diabetes, atherosclerosis, and cirrhosis of the liver. Traditionally, nutrition research has always been an important area of interest for NIH in general, and especially for NIADDK. Obesity and borderline malnutrition command increasing attention as serious pervasive problems, especially because of the role they may play in exacerbating other diseases. NIADDK supports basic, clinical, and behavioral research in the study of nutrition. Priority areas of investigation in this program include obesity, nutritional requirements in health and disease, nutritional support of hospitalized patients, the roles of fiber and trace elements in the diet, and basic studies of nutrient function.

KIDNEY, UROLOGIC, AND BLOOD DISEASES

Failure of the kidney to maintain the volume and composition of body fluids can lead to a variety of medical problems. These clinical conditions have often been well described, but the pathogenesis of most of them is poorly understood. With some exceptions, the progression of many chronic renal diseases is not significantly affected by therapeutic interventions, and their clinical management is often symptomatic and supportive. Death from chronic renal disease may be averted by the use of renal dialysis and transplantation, but even these therapies are imperfect. Therapeutic success is far from universal, often of limited duration, and frequently unpredictable. In addition, such therapy requires lengthy, repetitive, costly treatments.

NIADDK research efforts in kidney and urologic disease focus on the development of new methods of preventive therapy, early diagnosis, and more effective treatment through understanding of the basic mechanisms and causes of these disorders. These studies relate to normal structure and function of the kidney, metabolism, electrolyte transport and fluid dynamics, immune mechanisms, and the pathogenesis of a wide variety of renal disorders and urologic disorders including urolithiasis (renal stones) and other diseases of the lower urinary tract. These efforts provide hope that NIADDK's long-range goal of reducing the number of patients dependent upon artificial substitutes for normal kidney function will be realized.

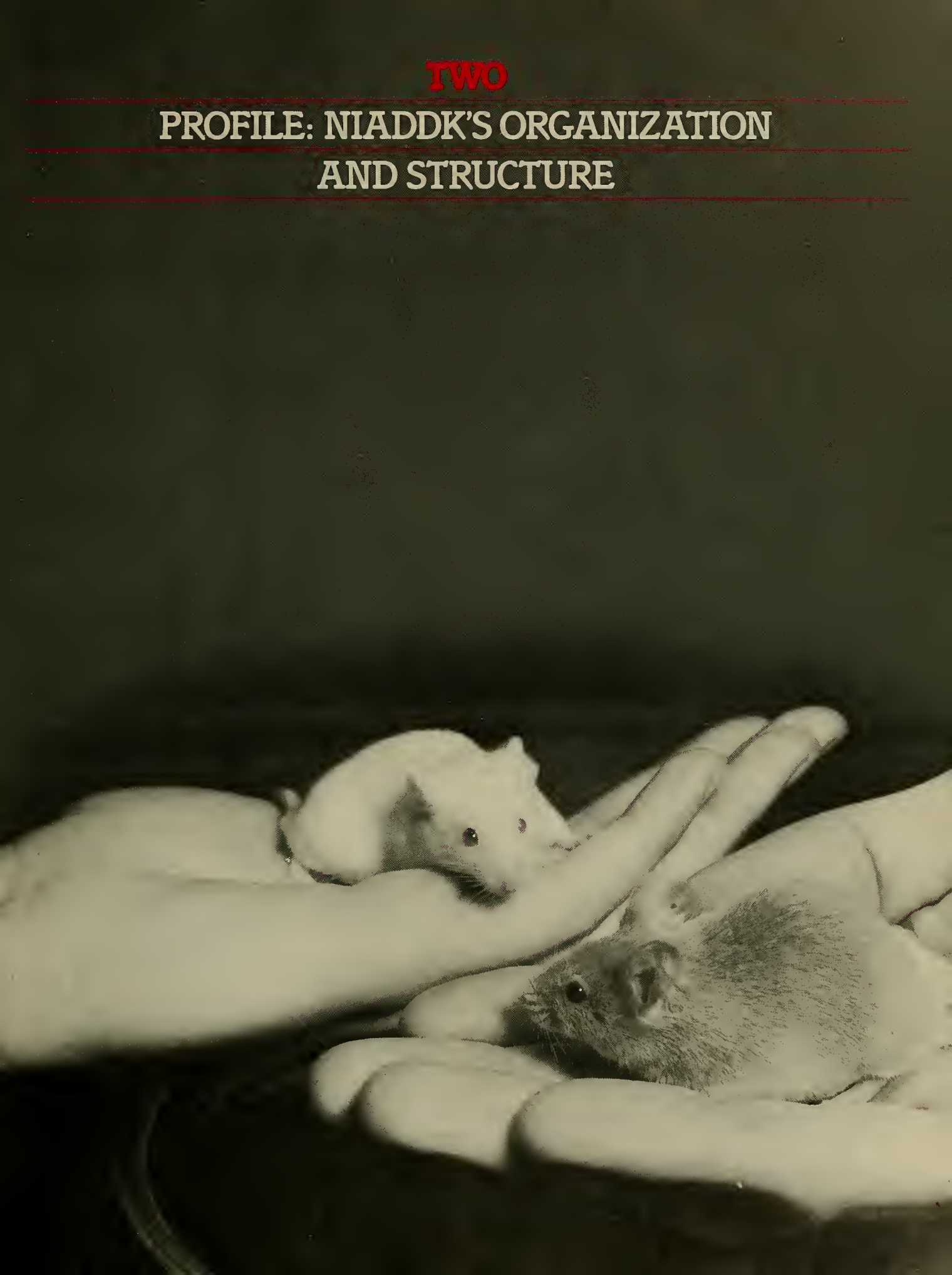
NIADDK also supports a program of hematologic research in normal blood cell function and the pathogenesis of various diseases affecting the red blood cell. This work encompasses a spectrum of studies from development of treatment modalities to clinical application and evaluation of treatment of relevant diseases and facilitates study of membrane phenomena and protein structure and function. This knowledge is applicable across a range of medical problems in areas such as chronic renal insufficiency, transplantation, and malignancy. Research priorities in this area include nutritional anemias, anemias of genetic origin, blood cell production disorders, metabolic disorders of iron transport and storage, and the immunology of blood-forming tissues, marrow transplantation, and autoimmune hematologic disorders.

MEETING THE CHALLENGE

Since President Truman's signing of the Omnibus Medical Research Act three decades ago, NIADDK's commitment to biomedical research has been confidently sustained and its involvement steadily expanded. Similarly, as the progress of research continues in the decades ahead, the Institute is prepared to keep pace by responding to current needs and identifying future opportunities. The result of this process is an evergrowing arsenal of methods to prevent or combat disease and improve the health of all Americans.

TWO

PROFILE: NIADDK'S ORGANIZATION AND STRUCTURE



Photographs

Page 1 - laboratory mice

Page 13 from top - X ray of [illegible] intramural research

[illegible] M.D. Studios, Inc.
[illegible] Weiss, Ed. 1976
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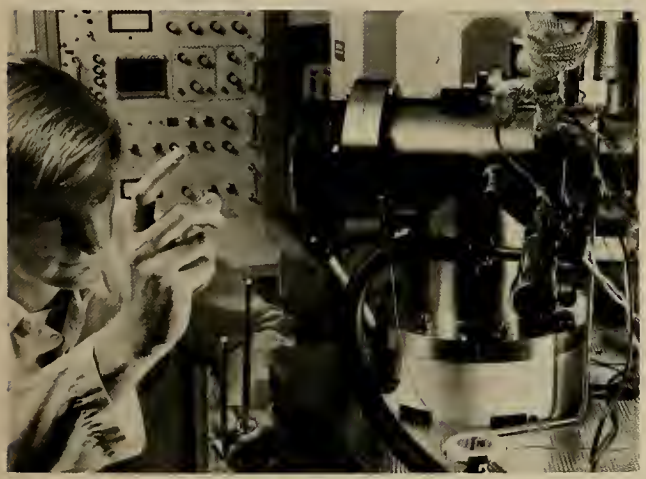
PROFILE: NIADDK'S ORGANIZATION AND STRUCTURE



As NIADDK moves forward in pursuit of knowledge and the development of more effective methods for improving the health of the American public, its organization and structure must rely on coordinated, interactive mechanisms that will produce responsive and substantive information. The current system under which NIADDK operates is designed to meet these essential requirements.

The current organizational structure of NIADDK (see figure 2) reflects its emphasis on basic biomedical and clinical research and research training. Institute efforts are planned and coordinated through both an intramural component, which focuses on research conducted primarily within NIADDK's laboratory and clinical facilities located on the NIH campus, and an extramural support program, which provides funding for research at universities, clinical facilities, and research institutions across the country and abroad.

The administrative and advisory activities of the Institute are organized to provide programmatic guidance as well as fiscal, analytic, and review services to facilitate the research effort. Other activities are aimed at developing and sustaining linkages to the scientific and health care community and also fall within the Institute's realm of administrative and advisory functions.

OFFICE OF THE DIRECTOR

The Office of the Director of NIADDK serves as the focal point for management and direction of Institute programs and operations. Because this office has ultimate responsibility for the information collected and disseminated through the Institute's programs, the Director and staff are involved in planning and coordinating the various activities of each of the Institute's programs.

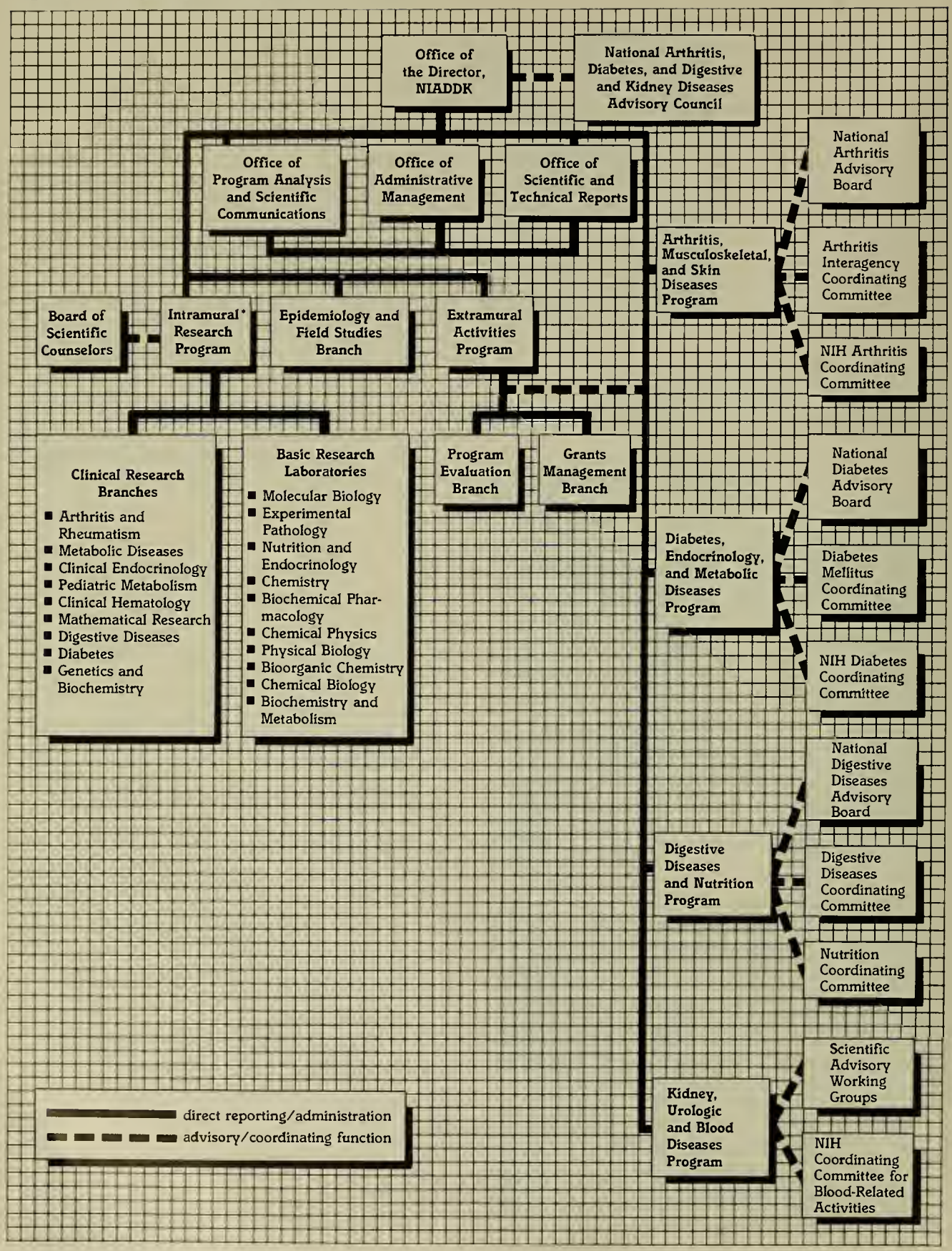
More specifically, the office directs the preparation of NIADDK plans and reports and provides policy direction and staff guidance in such areas as scientific program planning, administrative management, and utilization of resources. In addition, the Office of the Director is directly responsible for developing NIADDK's annual budget, which reflects the Institute's funding needs and resource priorities for its various activities—both program-related and administrative.

The Office of the Director also coordinates and prepares information needed by the Institute's Director to present and justify NIADDK's programs to the Director of NIH and to the Congress. These are ongoing activities that are mandated by the Institute's authorizing legislation so that progress achieved and problems encountered in NIADDK's various programs and activities can be continually assessed.

Administration and program components that provide assistance to the Office of the Director are the following:

- **Office of Administrative Management**—This office is integrally involved in the day-to-day

Figure 2.—Organization of NIADDK



*See figure 11 for detailed organization chart.

operations of the Institute. Its responsibilities are to plan and manage the Institute's budget and financial affairs, contracts, personnel, and office services.

- **Office of Program Analysis and Scientific Communications**—The primary functions of this office are the collection, processing, review, and evaluation of information about the Institute's programs. It also provides the Office of the Director with advice and counsel on the short- and long-term implications of evolving programs and policies as well as research accomplishments. This office is also the Institute's focus for legislative, program analysis, and reporting activities.

- **Office of Scientific and Technical Reports**—This office coordinates the preparation and distribution of information and publications concerning the Institute's activities and programs. The office works closely with other units of NIADDK to respond to the reporting and information needs of a variety of interested voluntary health and public interest groups, the Congress, and the public.

- **Extramural Programs**—Approximately 85 percent of Institute funds are utilized to support the Institute's extramural progress. The Institute's research and training support activities are administered as follows:

  - **Associate directors in charge of the four program clusters**–The associate directors coordinate and direct the activities of their respective programs areas. They also work closely with the Office of the Director in planning short-term and long-term research goals and initiatives. In addition, these individuals are responsible for monitoring and reviewing grant applications and reports to assure that the extramural research supported by the Institute is responsive to the mission and objectives of the Institute.

  - **Extramural Activities Program**–This office provides for the execution and administration of extramural awards and is under the direction of the associate director for extramural activities. These tasks are carried out with the assistance of the Program Evaluation and Grants Management Branches.

- **Intramural Research Program**—The intramural laboratory and branch chiefs are primarily responsible for directing the research activities conducted within the Institute's laboratories and clinical facilities. They work under the direction of the scientific director, who is responsible for the planning and coordination of the various research activities in the Institute's intramural program.

Each of these offices provides the substantive input that the Office of the Director requires to develop program plans and policies that are responsive to the Institute's long-term goals and objectives as well as to specific requests for information or studies mandated by Congress and the Administration. The Director's Office also relies on the expertise and advice provided by the National Arthritis, Diabetes, and Digestive and Kidney Diseases Advisory Council, a senior consultative body that is essential to the Institute's program organization and operations.

NATIONAL ADVISORY COUNCIL

The National Arthritis, Diabetes, and Digestive and Kidney Diseases Advisory Council is one of the national advisory councils established legislatively for the NIH, each an essential component of its respective Institute. The Institute's Advisory Council is composed of eminent scientists and experts in selected areas of biomedical research; civic leaders, educators, and lay persons with a specific interest in a particular disease or field of research in that disease; and representatives from DHHS and the Veterans Administration.

The functions and responsibilities of the National Advisory Council for NIADDK primarily consist of assisting the Office of the Director in overseeing the activities of the Institute, providing advice and counsel with regard to the Institute's goals and programs, and reviewing and approving or disapproving funding requests for extramural research grants following a primary peer review for scientific merit and feasibility. The Council is charged with assuring that the extramural research projects supported by NIADDK have a sound scientific basis, are relevant to the Institute's programs, and show promise of achieving results. Moreover, the Council's involvement in the planning and coordination of programs within the Institute provides it with an appropriate perspective for judging the merits of grant applications in light of NIADDK's overall priorities for research initiatives.

Members of the National Advisory Council are grouped into four subcommittees representing the four program areas that constitute the extramural research program. Members of the Advisory Council are assigned to the subcommittee most appropriate to their special scientific, education, or public affairs expertise in a particular disease area.

Each of the subcommittees is responsible for reviewing the substance of the extramural grant applications for research and training projects related to the diagnosis, prevention, and treatment of the diseases in its assigned area. Its recommendations on these grants and training awards are then presented to the full Advisory Council for further consideration and final approval. The subcommittees also review and evaluate the overall administrative activities of their respective clusters and suggest changes in program structure and operations when they deem such changes necessary.

OTHER ADVISORY AND COORDINATING GROUPS

In recent years, NIADDK's administrative, planning, and budgeting activities have been greatly influenced

by congressionally mandated advisory boards and coordinating committees for each of three specific disease fields—arthritis, diabetes, and digestive diseases. Each of these important bodies has contributed immensely to the Institute's coordinating, directing, and evaluating of research and training activities in the three disease areas.

NATIONAL ADVISORY BOARDS

Among the many recommendations in the plans submitted by the arthritis, diabetes, and digestive diseases commissions was the establishment of national advisory boards for each disease area. When formally designated, each of these boards was authorized by Federal law to monitor and facilitate the research, training, prevention, and control programs within its particular area of interest.

The primary functions and responsibilities of the National Arthritis Advisory Board, the National Diabetes Advisory Board, and the National Digestive Diseases Advisory Board are aimed at assuring that the directives outlined in each of the disease-specific long-range plans are effectively implemented. Each board is composed of 18 members representing a variety of scientific, educational, health care, and public service disciplines, and is required to accomplish the following:

- Review and evaluate progress in implementation of the plan developed for each relevant disease area;
- Periodically update the plans to assure their continuing relevance to the public's health needs;
- Provide advice and recommendations to the Secretary of Health and Human Services, the Director of the National Institutes of Health, the Director of NIADDK, and the heads of other appropriate Federal agencies for the implementation of each plan;
- Maintain liaison with other advisory bodies related to Federal agencies involved in carrying out the directives of the plans, coordinating committees for such diseases, and with other nongovernment entities involved in activities affecting the control of such diseases.

The advisory boards are also required by law to submit to Congress annual reports describing their activities during the preceding year, progress toward meeting the goals of the plans, government expenditures for activities in each disease area, and recommendations for changes in the plans, if appropriate. The reporting requirements are designed to keep Congress informed of all ongoing activities, issues, and anticipated needs in the areas of arthritis, diabetes, and digestive diseases.

INTERAGENCY COORDINATING COMMITTEES

NIADDK participates in interagency cooperation through three interagency coordinating committees, which are specifically responsible for fostering and improving research and health care programs in the areas of arthritis, diabetes mellitus, and digestive diseases. The interagency committees, which have been legislatively mandated for each of the three disease areas, serve an important role in facilitating communication among all Federal agencies directly or indirectly involved in their respective areas. Since their establishment in the mid-1970s, the committees have worked closely with the Institute's commissions and boards to develop improved approaches to information exchange, joint planning, and the identification of promising areas for cooperative undertakings.

The membership of each interagency coordinating committee consists of the pertinent associate director of the Institute's extramural research program, who serves as chairman, and representatives from selected Institutes within NIH, and from other Federal departments and agencies, such as the Veterans Administration and the Department of Defense, whose programs involve health functions and activities relevant to the disease areas addressed by the committees. Through these committees, the Institute has the opportunity and the capability to determine whether programs of research, health care, and related social services are adequate to meet the needs of those afflicted with arthritis and related diseases, diabetes, and digestive diseases.

TRANS-NIH COORDINATING COMMITTEES

Biomedical research comprises many highly technical and complex fields of scientific inquiry, requiring the knowledge and expertise of many trained investigators. Depending on the nature of the disease or health problem being addressed, the resources required to support adequate investigations may be beyond the capacity of any one Institute. Indeed, certain health issues or problems may span the program interests of several Institutes, thereby requiring a collaborative, cooperative effort to assure program balance and minimize duplication of activity.

NIH sponsors and conducts research in several categorical disease areas that touch upon the missions of most, if not all, of its Institutes and other organizational components. For these so-called trans-NIH topics, the Director of NIH may appoint a coordinating committee to provide a forum for exchange of information, a mechanism for coordination of individual programs, and a focus for policy development. The coordinating committees are composed of representatives of all of the appropriate Bureaus, Institutes, and Divisions (BIDs) within NIH, and their activities foster and supplement the continuing development of new research approaches in the participating NIH components.

The chairman of the coordinating committee for each area serves as a principal advisor to and representative of the Director, NIH, on all matters relating to that area. The chairman and other members may also participate in related interagency coordinating committees established by law or administration action.

Examples of such current trans-NIH committees are those for arthritis, diabetes, digestive diseases, nutrition, cystic fibrosis, genetic diseases, and epidemiology. The

following sections describe coordination efforts in several of these areas in which NIADDK plays a major role.

Arthritis

In 1977, the NIH Arthritis Coordinating Committee (ACC) was established with representatives from each of the BIDs having research interests in one or more aspects of the rheumatic diseases. The activities of the ACC were meant to complement those of the Arthritis Interagency Coordinating Committee (AICC) created by the National Arthritis Act. The committee's efforts are directed as follows:

- Strengthening and improving the NIH system for reporting on arthritis and related research, and coordinating these efforts with other Federal agencies;
- Identifying opportunities for joint sponsorship or workshops and symposia in selected areas of arthritis research;
- Providing a focus to stimulate productive research in this area and to coordinate it; and
- Exploring opportunities to promote the sharing of facilities and other resources for arthritis research.

Planning and emphasis are based on the missions, interests, and research program plans of the participating NIH BIDs, as well as on recommendations that were made by the National Commission on Arthritis and Related Musculoskeletal Diseases. Coordination among the NIH components has been achieved through joint program announcements, workshops, and conferences.

Diabetes

Because diabetes affects so many of the systems of the body, research programs in this area fall within the scope of almost all of the BIDs. Thus, the trans-NIH Diabetes Research Program was established in 1978 to facilitate cooperation in diabetes-related research programs and activities among all of the relevant Institutes at NIH.

The trans-NIH Diabetes Research Program is administered by the NIADDK associate director for diabetes, endocrinology, and metabolic diseases and is coordinated through the NIH Diabetes Coordinating Committee (DCC), which includes representatives from each of the NIH components involved with or related to diabetes research. The program is responsible for:

- Developing and maintaining a coordinated NIH plan to address the needs and opportunities in diabetes research, research training, data collection and analysis, and information transfer;
- Identifying research opportunities in all NIH and other Federal diabetes-related activities;
- Stimulating and coordinating the effort to gather epidemiologic data relevant to diabetes; and
- Serving as an information resource and the focal point for contact with other agencies or organizations.

Since its inception, the NIH Diabetes Coordinating Committee has initiated several activities. In 1978, and thereafter, eight Institutes issued an NIH-wide program announcement soliciting applications for research grants in diabetes and diabetes-related areas. These same Institutes, in 1978, solicited applications for research grants on the epidemiology of diabetes mellitus. In 1979, four NIH Institutes, in cooperation with the National Institute of Mental Health of the Alcohol, Drug Abuse, and Mental Health Administration, published a program announcement to encourage research grant applications dealing with the behavioral and psychosocial aspects of diabetes.

The NIH Diabetes Coordinating Committee has also fostered research manpower development programs. New awards emphasizing research on diabetes mellitus have been initiated and several others are planned for the near future. NIADDK and the National Heart, Lung, and Blood Institute (NHLBI) support a special emphasis research career award (SERCA) on the cardiovascular, endocrinologic, and metabolic implications of diabetes mellitus. NIADDK and the National Institute of Child Health and Human Development (NICHD) sponsor another such award to support research in the obstetrical, perinatal, and pediatric aspects of diabetes; and NIADDK and the National Institute on Aging (NIA) support awards related to aging and diabetes. In addition, each Institute supports research training, through national research service awards, in a broad range of biomedical, behavioral, and epidemiologic scientific disciplines related to diabetes.

Participants in the trans-NIH diabetes program work closely with the National Diabetes Data Group. The data group serves as the central point within NIH for the collection, analysis, and evaluation of epidemiological data that are fundamental to the development of sound scientific and public health policies related to diabetes and its complications. Members of the trans-NIH diabetes program also collaborate with the staff of the National Diabetes Information Clearinghouse, which is the national reference focus for diabetes information activities.

Nutrition

NIH is the primary agency in the Federal Government that conducts and sponsors research and training in nutrition as it relates to health maintenance, human development throughout the life cycle, disease prevention, and disease treatment. The NIH Nutrition Research Program involves all of NIH's BIDs that support nutrition-related research and is coordinated through its Nutrition Coordinating Committee (NCC).

The NCC consists of representatives from the participating NIH components as well as liaison members from other agencies of the Public Health Service, from the Office of the Assistant Secretary for Health, and from the Office of Science and Technology Policy in the Executive Office of the President. The trans-NIH Nutrition Research Program is administered by a special assistant to the Director, NIH, and the NCC is the

administrative focus for the coordination and review of nutrition research and research training priorities and also for the development of the NIH program in biomedical and behavioral research and training in nutrition. The coordination activity of the NCC not only minimizes duplication of effort among the NIH components, but also identifies areas in which research and research manpower in nutrition require further nurturing. Program announcements and requests for applications developed by the NCC and sponsored by more than one BID encourage activity in areas of perceived need in nutrition.

The NCC has developed a master nutrition plan for NIH that emphasizes research in four critical areas: clinical nutrition throughout the life cycle, the role of nutrition in disease development, prevention of disease, and treatment of disease. In addition to identifying research priorities, the nutrition plan includes emphasis on the transfer of modern nutrition technology, nutrition education for professionals and the public, training, and coordination of all these activities. NIADDK's contributions to these coordinated activities include the support of clinical nutrition research units (CNRUs) at several medical schools, the provision of leadership to the NCC Subcommittee on Nutrition Education, collaboration and planning for workshops related to nutrition, and the provision of reports on NIADDK nutrition activities for inclusion in the NCC annual report, "Program in Biomedical and Behavioral Nutrition Research and Training." In addition, NIADDK bears responsibility for administering the activities of the U.S. Malnutrition Panel of the U.S.-Japan Cooperative Medical Science Program, which seeks to identify needs and opportunities for collaborative nutrition research on an international scale, and administers and funds, through NIH, a number of malnutrition-related research grants and contracts.

Cystic Fibrosis

Because of the multidisciplinary nature of cystic fibrosis (CF) research, support and management of CF-related investigative efforts are shared among several BIDs of NIH. A Cystic Fibrosis Coordinating Committee, consisting of representatives from the various NIH components involved in the support of CF-related research activities, coordinates the overall course of investigations to avoid duplication of effort and to identify more readily the specific research and manpower requirements in this field. Program leadership is executed through the extramural Endocrinology, Metabolic Diseases, and Resources Program Branch of NIADDK.

Through the coordinating committee, a major program was initiated to increase researcher awareness of the many challenges and opportunities inherent in the study of cystic fibrosis. To apprise the scientific community of these opportunities, NIADDK participated in the development of an NIH-wide cystic fibrosis announcement to encourage the submission of research grant proposals in key CF research areas. In addition, a brochure entitled "CF: A Disease in Search of Ideas," outlining research needs, was distributed to over 30,000 scientists. As a result of these efforts, the number of applications requesting support of CF investigations has nearly tripled.

Blood-Related Activities

Support and management of blood-related research activities are shared among several Institutes of NIH. The NIH Coordinating Committee for Blood-Related Activities coordinates the overall course of investigations in the area of blood research and the use of blood resources. The membership of the coordinating committee represents six Institutes at NIH, including NIADDK, as well as the Division of Research Resources at the NIH Clinical Center. The director of the Division of Blood Diseases and Resources of the National Heart, Lung, and Blood Institute serves as the chairman.

One of the major goals of the committee is preparation of a directory of blood-related research projects conducted and supported by NIH (and, ultimately, by the Federal Government and nongovernmental sources). NIADDK shares in this and other coordination efforts through active participation by the Institute's hematology program director.

BOARD OF SCIENTIFIC COUNSELORS

NIADDK's Board of Scientific Counselors was initiated in 1956 and currently operates under the statutory authority of P.L. 92-463, serving as an internal review committee responsible for monitoring the activities of the Institute's Intramural Research Program. Establishment of this group was considered essential to ensure that unbiased, extragovernmental expert review of intramural research activities would be provided. In effect, the activities of the board were developed in parallel with the review mechanisms established for the extramural research program.

The board consists of eight members, each representing a field of research or scientific discipline related to the basic clinical research activities of the Institute. Members meet twice a year to visit the Institute's laboratory facilities, review scientific reports on progress and accomplishments achieved through research activities, and make recommendations to the scientific director, the Director of NIADDK, and the Director of NIH concerning the Intramural Research Program. In addition, the board is required to submit an annual report on its activities and findings to the Secretary of HHS, the Assistant Secretary for Health, and the Director of NIH.

RESEARCH PROGRAMS

INTRAMURAL RESEARCH

The Intramural Research Program covers a wide range of disease investigations within the Institute's laboratory and clinical facilities on the NIH campus. The broad disease areas of arthritis and related musculoskeletal disorders, endocrine and metabolic disorders,

digestive and nutrition-related disorders, and kidney and blood disorders are addressed through basic research involving biochemistry, nutrition, pathology, microbiology, immunology, pharmacology, and a host of other basic science disciplines which contribute to our understanding of disease processes.

Intramural research activities are organized into 9 branches engaged primarily in clinical research (on arthritis, diabetes, etc.) and related activities; in addition, 10 laboratories and related sections, engaged primarily in basic research related to the Institute's categorical disease responsibilities, are organized along scientific discipline lines (molecular biology, experimental pathology, etc.). The nine branches consist of the following:

- **Arthritis and Rheumatism Branch**—Conducts clinical and laboratory investigations into the etiology, pathology, and pathogenesis of such diseases as rheumatoid arthritis, degenerative joint diseases, gout, fibrositis, and other related arthritis disorders. Specific attention is directed to the development and evaluation of medications and therapeutic devices and procedures, prevention and diagnostic instruments, and other procedures to control, treat, or ameliorate the effects of these disorders.
- **Metabolic Diseases Branch**—Conducts clinical and laboratory research into the physiology and nature of metabolic diseases and disorders. Emphasis is given to the measurement of total human energy metabolism and those factors that disturb or disrupt metabolic energy, and to studies involving mineral metabolism.
- **Clinical Endocrinology Branch**—Conducts research on the biochemistry and metabolism of hormones and endocrine glands and the effects of the hormones on tissue.
- **Pediatric Metabolism Branch**—Conducts clinical and laboratory investigations into diseases and disorders of metabolism that affect children, such as cystic fibrosis, celiac disease, and related anomalies.
- **Clinical Hematology Branch**—Conducts clinical and laboratory research into diseases and disorders of the blood, such as hemophilia, with specific emphasis on factors that contribute to disturbances in various elements of the blood.
- **Mathematical Research Branch**—Conducts research on the mathematical and theoretical aspects of biological problems. Consulting services are also available to Institute staff and other NIH investigators interested in applying mathematical techniques to their research projects.
- **Digestive Diseases Branch**—Conducts clinical and laboratory research into diseases and disorders of the digestive tract. Efforts are directed to research on the physiology, biochemistry, and etiology of diseases of the gastrointestinal tract and the liver, enzymes and metabolic pathways, disturbances in gastrointestinal tract function, and the effect of various treatments and therapies.
- **Diabetes Branch**—Conducts research on diabetes mellitus and other related endocrine diseases. Investigations concentrate on the nature and etiology of insulin and growth hormone and those factors that contribute to disorders or disruptions in these natural processes.
- **Genetics and Biochemistry Branch**—Plans and conducts laboratory and clinical investigations of abnormalities in proteins produced in genetic diseases, the fundamental problems of mammalian genetics, and the immunochemistry and cell biology of problems related to cell differentiation and organization.

A related group, the Epidemiology and Field Studies Branch, develops and applies epidemiologic methodologies in the investigation of arthritis and metabolic diseases. These activities involve the conduct of field studies on selected populations throughout the United States and the provision of assistance to scientific investigators engaged in research on arthritis and related metabolic disorders.

The 10 laboratories of the intramural program are:

- **Laboratory of Molecular Biology,** with sections for physical chemistry, molecular structure, metabolic enzymes, organic chemistry, molecular genetics, theoretical molecular biology, and microbial genetics.
- **Laboratory of Experimental Pathology,** with sections for chemical pathology, cellular function and ultrastructure, cytogenetics, biophysical histology, and molecular pathology.
- **Laboratory of Nutrition and Endocrinology,** with sections for endocrinology, membrane regulation, nutritional biochemistry, developmental biochemistry, and vitamin metabolism.
- **Laboratory of Chemistry,** with sections for microanalytical services and instrumentation, medicinal chemistry, metabolites, carbohydrates, and biochemical mechanisms.
- **Laboratory of Biochemical Pharmacology,** with sections for pharmacology, biochemistry of cell regulation, biochemistry of amino acids, biochemistry, and physical biochemistry.
- **Laboratory of Chemical Physics,** with sections for spectroscopy and structure, molecular biophysics, membrane biophysics, macromolecular biophysics, and nuclear magnetic resonance.
- **Laboratory of Physical Biology,** with sections for comparative physiology and cellular physics.
- **Laboratory of Bioorganic Chemistry,** with sections for pharmacodynamics and oxidative mechanisms.
- **Laboratory of Chemical Biology,** with sections for protein chemistry, macromolecular biology, and protein conformation.

- **Laboratory of Biochemistry and Metabolism,** with sections for enzymes and cellular biochemistry and intermediary metabolism.

Intramural program direction is provided through the various evaluative and analytical activities that affect the allocation of funds, personnel, and space for offices and laboratories. Collaboration with other NIH programs and national research efforts in related areas enhances the assimilation of new research techniques into the overall program structure. Moreover, because the intramural program constitutes such an important component of NIADDK's activities and responsibilities, ongoing and planned research efforts are considered in program planning by the Institute's other organizational units.

EXTRAMURAL ACTIVITIES

The extramural program comprises investigations that are funded by the Institute but are conducted at universities, private and public research facilities, and hospital-based clinical research centers throughout the Nation and in other countries. Grants and contracts are the mechanisms that NIADDK uses to generate and administer extramural project activities in the four disease clusters.

Each of the program clusters functions as a distinct administrative unit with responsibility for the allocation and management of research funds through research grants, contracts, fellowships, training grants, and special awards to qualified applicants and institutions. Activities supported range from basic and applied research investigations including clinical studies to training programs in fundamental and clinical sciences. The chart on page 21 describes the various types of award mechanisms available to grantees and contractors through the Institute's Extramural Activities Program.

The testing for safety and efficacy of an emerging technique, drug, device, or procedure is generally accomplished through NIADDK's clinical trials program. Some examples of clinical trials currently or recently supported by NIADDK include the following:

- Long-term toxicity study of PUVA for psoriasis;
- Therapy in severe lupus nephritis;
- Safety and clinical effectiveness of oral retinoids in dermatological disease;
- Evaluation of selected modes of therapy of osteoporosis;
- Cooperative systematic studies in the rheumatic diseases;
- National Cooperative Gallstone Study; and
- Efficacy of control of blood glucose concentration and the development of complications of diabetes mellitus.

The Institute's extramural program funds and coordinates each trial over its full course, which may be several years. Population samples for a particular clinical trial may involve several thousand people from across the Nation or a few hundred residents of a single community. The results of these trials provide valuable information concerning the advisability of using the subject drug, device, or procedure in the health care setting. Sometimes, a procedure may prove to be very effective, but its cost may be so high that practical application on a large scale would not be feasible. In such cases, clinical trials may point up the need for further research to reduce the expense associated with use of the technique.

SPECIAL PROGRAMS

Just as the Institute's research and disease responsibilities are many and varied, so too are the available opportunities to foster collaboration among scientists across the Nation and around the world to further research and apply new knowledge. Over the years, NIADDK has developed and implemented special programs to expand research opportunities and services, which have enabled the Institute to reach beyond the realm of the laboratory to the community where those afflicted with disease and those who treat them may benefit more quickly from current progress.

NIADDK'S CENTERS PROGRAMS

In addition to providing support to institutions and organizations for the traditional research and research training programs, the Institute also has responsibility for a program of "center" facilities. Through the centers programs, some of which were specifically authorized by legislation in the mid-1970s, institutions have been competitively selected to provide a variety of multidisciplinary approaches to research, education, and community demonstrations in arthritis and related musculoskeletal diseases, diabetes, endocrine and metabolic disorders, digestive diseases and nutrition-related problems, and specialized research into kidney and urologic disorders. Currently active centers are listed in chapter VII.

NIADDK sponsors 21 Multipurpose Arthritis Centers (MACs) across the country. The MACs are engaged in activities that address all phases of the arthritis problem, from basic research in the causes of the disease and pilot and feasibility studies for developing investigators, to education and training and the community application of evolving methods of treatment.

The diabetes centers program consists of two types of facilities: Diabetes-Endocrinology Research Centers (DERCs), which concentrate on basic and clinical investigations conducted in a core setting of shared, comprehensive laboratory facilities; and the Diabetes Research and Training Centers (DRTCs), which encompass basic and clinical research as well as the education and training of new investigators and the translation of research results into improved care and management of diabetic patients. For added research incentive, both DERCs and

NIADDK Extramural Program Award Mechanisms

- **Research project grants**—An institution is awarded a grant on behalf of a principal investigator to facilitate pursuit of a scientific initiative or objective in the area of the investigator's interest and competence Applications are accepted for health-related research and development in all areas within the scope of the Institute's mission. This is the largest single support mechanism utilized by NIADDK

- **Program project grants**—Program project grants are awarded to an institution on behalf of a principal investigator for the support of a broad-based, often multidisciplinary, long-term research program with a particular major objective or theme. The type of project supported with this award involves the organized efforts of groups of investigators who conduct research projects related to the overall program objective. Each project supported under a program project grant is expected to contribute to the overall program objective

- **Center grants**—Center grants are awarded to institutions on behalf of a program director and group of collaborating investigators to provide support for long-term, multidisciplinary programs of research and development However, center grants are more likely to have a clinical orientation than are program project grants and are usually developed in response to announcements of specific program needs and requirements of the Institute

- **Resource awards**—These awards provide support for research resources such as computer centers or general clinical research centers operating on an institutional, regional, or national basis. While the resources normally serve a wide range of biomedical research, they may be oriented toward specific research needs.

- **Conference grants**—Conferences planned for the purpose of coordinating, exchanging, and disseminating scientific research information related to the Institute's program interests may be supported by conference grants. Generally, the awards are provided for cooperative participation with other organizations in the support of conferences rather than for provision of sole support

- **Research contracts**—Contracts are offered for specific research problems that have been identified by the Institute and that require central direction, control, and management Clinical trials of new or established therapies may be funded by this mechanism.

- **Development contracts**—These contracts, which are rarely used, are awarded for projects to produce substances, devices, systems, or other approaches to diagnose, prevent, treat, or control diseases. Examples of such projects include the development of effective vaccines or drugs, surgical techniques or medical devices to assist or replace organ functions, and sophisticated instruments to refine laboratory or clinical procedures.

- **Demonstration contracts**—These contracts are awarded to support projects designed to demonstrate the feasibility of applying biomedical research advances or technologies to individual or community situations to solve certain health problems.

- **Research and development support**—Awards in the research and development category are offered to finance certain resources or services to aid ongoing activities. These include data processing, drug testing, toxicology screening, logistics services, and collection and distribution of materials needed to conduct biomedical research and development.

- **Scientific communication and evaluation awards**—These awards are provided to support special conferences, workshops, and seminars that are planned to analyze the significance of new biomedical research findings and for developing a scientific consensus on those findings.

- **Manpower training awards**—A detailed description of the mechanisms used by the Institute to support manpower development is provided in chapter V.

DRTCs provide limited funds for pilot or feasibility studies to encourage young investigators and promote innovation in research concepts.

The digestive diseases and nutrition cluster sponsors seven centers that support and conduct basic and clinical investigations of a variety of health problems related to its program areas. One such center conducts research on liver disease, the effect of drugs and injuries on the liver, and the etiology of disease processes, while a second center is studying diet and eating behavior that contributes to obesity, a model program that is intended to foster multidisciplinary research and exchange of information. The Institute is also currently supporting five clinical nutrition research units, which serve as focal points for multidisciplinary research in clinical nutrition as well as provide for the development of programs in clinical nutrition which enhance the education of various health professionals.

NIADDK has also supported Specialized Centers of Research (SCORs) in urolithiasis (kidney stone disease). These centers focused resources, scientific expertise, and facilities on research into basic mechanisms responsible for urolithiasis and its multiple causes. Other goals included delineation of effective therapy for

patients and development of rational methods for the prevention of kidney stones.

The Institute's centers programs provide an important link between NIADDK, the scientific community, and the health care delivery system. The application of new and evolving techniques for research and treatment remains an important function of the Institute as it strives to meet its overall program objectives.

A PROGRAM FOR INTERNATIONAL COOPERATION

As an integral component of NIADDK's biomedical research program, a number of collaborative and individual research efforts have been supported which draw upon the talents and investigative expertise of the international scientific community. Through the Bilateral Cooperative Agreements Program, NIADDK has developed collaborative and cooperative activities with Japan and the U.S.S.R. in a number of relevant fields.

U.S.-Japan Cooperative Program in Malnutrition

Since 1966, the U.S.-Japan Cooperative Medical Science Program has been actively engaged in collaborative research efforts to develop greater understanding of the effects of malnutrition on physical growth, mental development, and performance. These activities and projects are carried out through cooperative arrangements developed between the United States and Japan, which share responsibility for the program.

Research continues to be the primary focus of activities supported by the malnutrition program panel. Studies have been developed and conducted abroad among populations with severe nutritional deficiency diseases and are designed to find solutions to complex malnutrition problems. The availability of large population groups afflicted with nutrition disorders provides NIADDK and the other sponsoring members of this program with valuable information and insight into the many aspects of malnutrition and its implications for health and well-being.

Under the administrative direction of NIADDK's Digestive Diseases and Nutrition Program, the malnutrition program panel has sponsored a number of symposia devoted to special priority topics concerning nutrition research and diseases caused by malnutrition, as stated in joint scientific guidelines. The priority areas have been revised and modified from time to time, depending on the advances in research and the need for change of direction and emphasis.

U.S.-U.S.S.R. Cooperative Program in Arthritis

The origins of the U.S.-U.S.S.R. arthritis program can be traced to the Health Exchange Program of 1972, a joint agreement developed to improve collaboration in the field of public health and medical science. In September 1973, arthritis became the fourth major cooperative project in the health sciences under this program.

The program emphasizes clinical studies using commonly agreed-upon protocols. More than 10 meetings have been held between the members of the cooperating research centers. The meetings, which featured discussions of preliminary study results and future projects, have been supplemented by the exchange of reprints and lecture materials.

Research projects supported by this program have been largely studies on the use of drug intervention in the treatment of rheumatoid arthritis. Other projects include microbiological and immunological investigations in systemic lupus erythematosus and the role of orthopedic surgery in the treatment of arthritis.

NATIONAL HORMONE DISTRIBUTION PROGRAM

Initiated in 1963 with Institute funds and interest and support from the College of American Pathologists, the National Hormone Distribution Program (NHDP) has provided supplies of human growth hormone for use in the treatment of metabolic and growth disorders arising from disruptions in secretion of the hormone from the pituitary gland. Extracts of human growth hormone from pituitary glands collected at autopsy have, to date, provided the only source of treatment of hypopituitary dwarfism.

As research into methodology advanced over the years, it was found that other anterior pituitary hormones could be extracted from the same glands without loss of human growth hormone. The scope of the NHDP was therefore expanded to provide for the distribution of these hormones, including follicle stimulating hormone, luteinizing hormone, thyroid stimulating hormone, prolactin, adrenocorticotropic hormone (ACTH), and lipotropin.

The program also develops and distributes many antisera to the various pituitary hormones. These substances, which generally have been rarely available, have proven to be invaluable in many extensive programs of basic and clinical investigation.

TECHNOLOGY TRANSFER: NIADDK AT THE HEALTH CARE INTERFACE

Unless the knowledge gained through basic and subsequent clinical research is diffused in the scientific and health care communities, the value of that research is significantly limited. Therefore, in addition to its research activities, NIADDK, like the other Institutes within the NIH community, also maintains programs to foster the application and demonstration of new and evolving research techniques and disease interventions. The development and testing of mechanisms to facilitate the transfer of knowledge to those involved in providing care to the public are integral to that effort.

The Institute uses a number of channels to promote the diffusion of information and the transfer of technology:

- Dissemination by the Office of Scientific and Technical Reports of technical, educational, and

informational publications on topics such as
  - advances in research techniques and treatment methodologies
  - disease descriptions
  - training information
  - program reports;
- Collection, storage, maintenance, preparation and dissemination of publications, audiovisual materials, and other information through the Institute's clearinghouses;
- Support of and participation in workshops, seminars, and conferences for scientists, health care providers, and other health professionals; and
- Technical consensus development conferences, sponsored in conjunction with the Office for Medical Applications of Research (Office of the Director, NIH), for the purpose of assessing the safety, efficacy, cost-effectiveness, and feasibility of health care technologies, both those that are emerging and those in widespread use.

INFORMATION DISSEMINATION

The successful transfer of a given technology from the basic or applied research stage to its clinical application depends largely on the availability of information about that technology. Through its Office of Scientific and Technical Reports, NIADDK disseminates a variety of materials on the technologies, drugs, procedures, and devices being developed through its research programs, as well as printed matter designed to educate and inform the general public about the health problems that the Institute addresses. Such activities are of obvious importance in promoting health and preventing disease—critical objectives of all of the NIH Institutes.

NIADDK'S CLEARINGHOUSES

Arthritis Information Clearinghouse

One major component of the Institute's information dissemination program is the Arthritis Information Clearinghouse. Authorized by the National Arthritis Act, following a recommendation by the National Commission on Arthritis and Related Musculoskeletal Diseases, the clearinghouse is designed to improve the lines of communication among the health professionals serving the arthritis patient. The major function of the clearinghouse is to collect, screen, store, and disseminate information about educational materials and programs in the rheumatic diseases.

In serving as a broker to facilitate the flow of information about arthritis, thus helping users to locate and select educational materials, the clearinghouse refers clients to appropriate developers or sources rather than acting as a distributor of the materials. The arthritis clearinghouse data base consists of 1,800 records, including print and audiovisual materials, journal articles, reports, textbooks, and other items.

National Diabetes Information Clearinghouse

The National Diabetes Information Clearinghouse (NDIC) was established in September 1978 to serve as the central resource for the collection and dissemination of information about educational and scientific materials, programs, and other resources relevant to diabetes. To this end, the clearinghouse strives to increase the availability of information for health care professionals, for patients, and for their families; increase community awareness and understanding of diabetes as a major health problem; and establish a viable system for speedy communications about new developments, techniques, and programs in diabetes among all sections of the diabetes community. Since its inception, the clearinghouse has abstracted and indexed almost 2,500 educational brochures, booklets, and other materials on diabetes for health care professionals, people with diabetes, and the general public.

Bibliographic listings prepared by the clearinghouse not only provide information but also identify areas needing more educational materials. An example is the severe shortage of diabetes information for adults with limited reading ability as well as materials for minority populations. NDIC provided needed support to the Indian Health Service to develop and field test a diet manual for one such group, the American Indians living in the southwestern United States.

NDIC continues to cooperate closely with other Federal agencies as well as state agencies, voluntary organizations, and health professionals in order to develop strategies to increase community awareness and understanding of diabetes as a major health problem and to encourage effective patient, family, and community educational programs.

National Digestive Diseases Education and Information Clearinghouse

The National Digestive Diseases Education and Information Clearinghouse (NDDEIC), formally authorized under P.L. 96-538, the Health Programs Extension Act, has been serving as a national educational resource for patients with digestive diseases and their families, as well as physicians, health professionals, and the general public. The program is specially designed to reach neglected population groups, such as the elderly, minority groups, rural Americans, and children.

The primary objective of the NDDEIC is to bridge the communication and information gap that currently exists between those who are developing knowledge about digestive diseases through research and those who suffer from the effects of these disorders or who direct their care. Physicians, nurses, and allied health professionals also need to be informed about the availability of treatments, medications, and other interventions that have been developed for use in the clinical care setting. To this end, the clearinghouse has evolved as a national center of educational and information materials that have been developed for all segments of the public concerned or affected with digestive diseases.

These materials range from technical information manuals designed for use by physicians and health professionals to audiovisual presentations developed especially for elementary school children.

The activities of the NDDEIC also include a comprehensive system for data collection, storage, and retrieval. This system facilitates the dissemination of basic information concerning these diseases to the general public as well as reference citations to medical students, research scientists, health care professionals, and educators.

SCIENTIFIC CONFERENCES AND CONSENSUS DEVELOPMENT

Rapid advances in technologies, treatment procedures, or methods of diagnosis and prevention necessitate that the Institute maintain close contact with those who share an interest in its research areas. NIADDK therefore participated in approximately 80 national and international conferences, workshops, and seminars during 1980. The subjects of discussion ranged from the molecular structure of proteins to the pathology of skin diseases. The opportunity to meet and exchange information about the latest research and health care techniques brings eminent scientists, researchers, physicians, and other health care professionals together from across the Nation and around the world. Such meetings also offer excellent opportunities for NIADDK to present reports on advances achieved through its basic and clinical research programs.

NIADDK has actively participated as well in the NIH consensus development program by which various concerned parties are brought together under the umbrella of a technical consensus development conference to seek general agreement on the safety, efficacy, and appropriate conditions for use of various medical procedures, drugs, and devices.

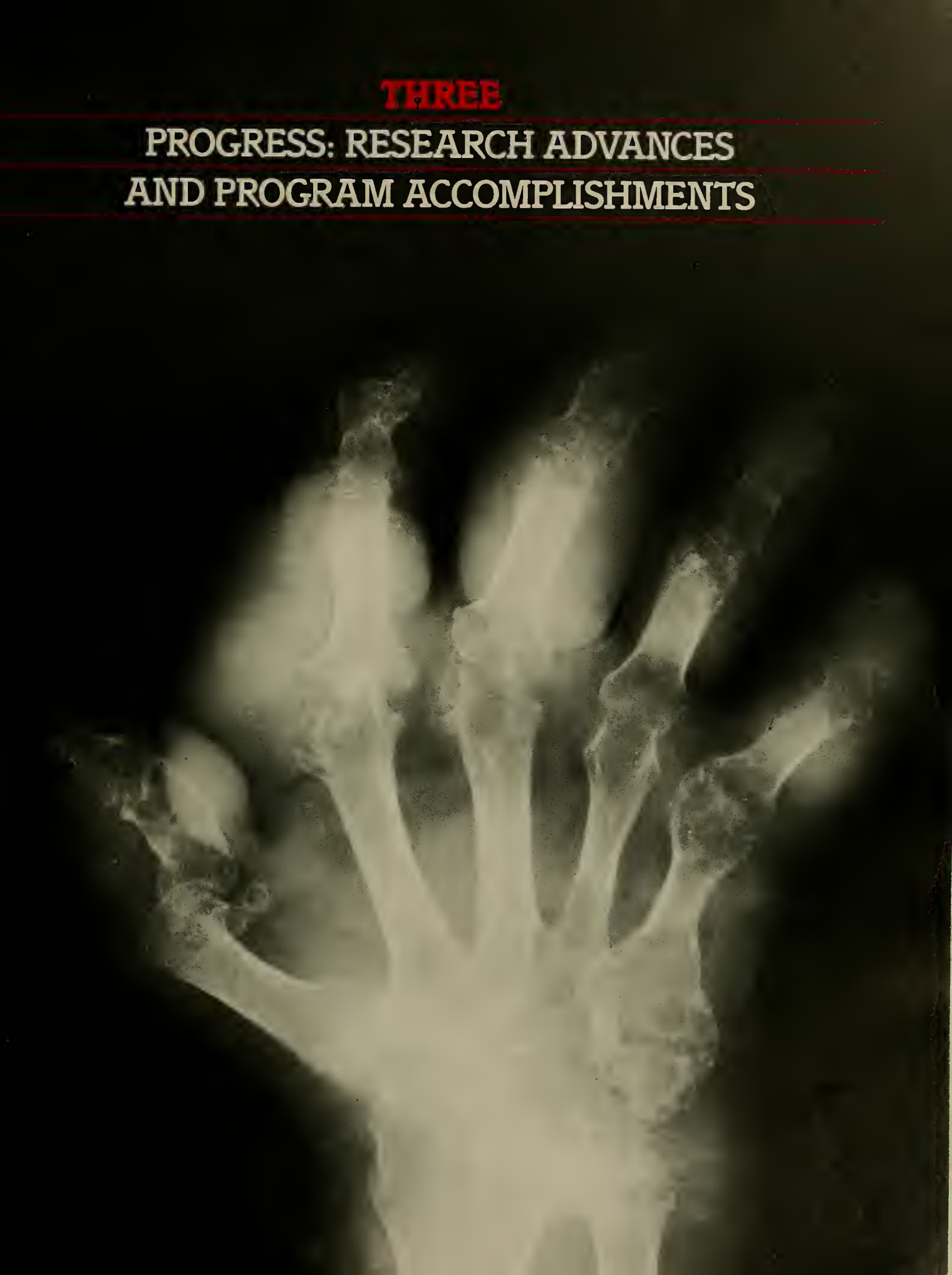
In December 1979, NIADDK organized such a conference on the surgical treatment of morbid obesity in order to consolidate and evaluate the state of the art in this controversial field. In the summer of 1980, NIADDK sponsored a consensus development conference on the advantages and disadvantages of endoscopy and its use as a nonsurgical diagnostic procedure for detecting the source of acute bleeding in the upper gastrointestinal tract.

* * *

NIADDK thus supports all phases of research and development of health care techniques and technologies from the conception in the mind of a scientist through applications in the hospital or clinical setting. Every effort is made to keep the interests of those who suffer from the diseases and disorders within the Institute's realm of responsibility at the forefront of research, administrative, and planning decisions.

THREE

PROGRESS: RESEARCH ADVANCES AND PROGRAM ACCOMPLISHMENTS



PROGRESS: RESEARCH ADVANCES AND PROGRAM ACCOMPLISHMENTS

INTRODUCTION

For centuries physicians have been able to treat the symptoms of disease, but only in recent years have the means for curing or preventing certain diseases become available. The effectiveness of such curative or preventive therapies is usually directly related to the level of understanding of the basic disease process. In this century, the rapid rate of technological development has, in many cases, surpassed our level of basic understanding of disease, leaving gaps in our knowledge. Physicians now have available to them effective techniques to attack the symptoms of certain diseases, yet still may not understand or be able to deal effectively with the underlying disease processes. As a result, the new therapies are often quite expensive and frequently yield less than optimal results.

Clearly, hope for more effective treatment and prevention lies in research into the basic nature of diseases and the mechanisms by which they alter normal body function. NIADDK capitalizes on a wide range of scientific expertise and technologically advanced research capabilities in the pursuit of answers to the difficult questions posed by the chronic, disabling diseases within its purview.

While investigators performing fundamental studies seek new clues to the cause of disease, clinical researchers are applying existing knowledge to alleviate the pain, disability, and suffering of patients. This latter goal focuses on the development of improved diagnostic methods, more effective medical, surgical, and pharmacologic treatments, and improved rehabilitation techniques. Aside from the humanitarian aspects of prevention or improved management of diseases that cause much human suffering, it is hoped that these efforts will lead to a reduction in the economic impact of these diseases and the high cost of their treatment.

Many times throughout its existence, the Institute has been confronted with the realization that unilateral pursuit of a disease problem along purely clinical or applied lines sooner or later reaches a point of rapidly decreasing returns because of serious limitations in fundamental knowledge about the disease and its etiology. Building on these experiences, the Institute endeavors to maintain an appropriate balance in the allocation of its resources among fundamental investigations, clinical studies, and specifically directed developmental research. No single inflexible formula for such allocations exists. The state of the art of research among the Institute's various disease categories changes rapidly with the passage of time. A process of continually analyzing the state of the art is necessary to the formulation of appropriate decisions about program allocations. This constant program analysis by the Institute staff and advisors is an essential component of a meaningful and responsible research policy.

Growth of knowledge has proceeded at a rapid pace, in a relatively short time, in all arenas—basic research, clinical investigations, applied research and development—and these efforts, when translated into professional education, medical practice, and prevention and

control programs, have yielded enormous benefits in the improvement of the quality of human life.

This chapter reports on progress in our understanding of human health and disease in the 30 years since NIADDK's establishment. The discussion for each program area presents a general description of the types of research being conducted, a brief listing of the most recent and noteworthy advances in the research ("Highlights of Recent Advances"), and a summary of the knowledge gained through NIADDK-supported investigations over time ("Pathways of Research Progress").

ARTHRITIS, MUSCULOSKELETAL, AND SKIN DISEASES

ARTHRITIS AND RELATED DISORDERS

Arthritis and related diseases afflict nearly 32 million people in the United States and cause an estimated annual loss of about $17 billion to the economy. During the last three decades, however, these chronic, crippling diseases have yielded significant ground to intensified research.

NIADDK research efforts in arthritis and related disorders are vigorous and diverse. Through its extramural grant and contract programs, the Institute supports research at major universities and medical schools throughout the country. At the same time, NIADDK conducts intensive intramural research in its Arthritis and Rheumatism Branch at the Clinical Center of the National Institutes of Health in Bethesda, Maryland.

Among the more than 100 kinds of arthritis and related rheumatic diseases are such disorders as rheumatoid arthritis, degenerative joint disease (osteoarthritis), systemic lupus erythematosus (SLE), gout, and many inherited and acquired connective tissue disorders. As the underlying causes of these disorders remain elusive, basic research is fundamental to the development of effective preventive and therapeutic approaches to the bone and joint disorders.

Institute-supported studies on arthritis make use of a wide range of scientific expertise and technologically advanced research capabilities. For example, many projects employ highly sensitive biochemical methods to analyze bone tissue, the lubricative lining of joint cavities, and the components of cartilage, the tough connective tissue attached to joint surfaces. These studies are yielding substantial new knowledge about protein and enzyme interactions, cartilage metabolism, bone mineralization, and the roles of physiologic and metabolic processes in maintaining healthy joints.

Another major avenue of NIADDK arthritis research involves the discipline of immunology, the study of an organism's ability to fight off external disease-producing agents through its immune system. Research has demonstrated that typically protective antigen-antibody reactions can go dangerously awry, causing an organism to produce antibodies that attack its own tissues or tissue components. Results from several studies suggest that this phenomenon, called autoimmunity, is implicated in systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, polyarteritis, and other rheumatic diseases. With the discovery of the importance of immunogenetics to the rheumatic diseases, scientists are now actively seeking to identify specific types of tissue antigens that may serve as "markers," or advance warning signals, for detecting a healthy individual's susceptibility to the development of rheumatic disease.

While basic investigators seek new clues to the cause of arthritis, clinical researchers are applying existing knowledge to alleviate pain and disability and improve rehabilitation. This work centers on the development of improved drug therapies and other medical technologies. In the area of pharmacology, for example, researchers are continuing to study the action of anti-inflammatory drugs, such as corticosteroids, salicylates, and the newer nonsteroidal anti-inflammatory agents, as well as medications that suppress the body's immune response. A primary aim is to enhance a drug's beneficial effects while minimizing its toxic or other adverse consequences. Unfortunately, many potent antiarthritic agents can produce serious side effects when administered in the dose and frequency required to counteract the symptoms of arthritis. Thus, pharmacologists and rheumatologists are searching for ways to localize drug action at specific disease sites, thereby avoiding possible toxic effects in other parts of the body.

Highlights of Recent Advances

The following highlights describe recent NIADDK-supported advances against arthritis and related diseases, which have led to an increased understanding of these disabling disorders and an improved ability to detect, treat, and prevent them:

- Long-standing and crippling rheumatoid arthritis complicated by severe vasculitis can be successfully treated with the drug cyclophosphamide.
- Evidence has been accumulated that indicates that some types of juvenile arthritis may be inherited.
- Antisera capable of detecting SLE-specific antigens in the serum of patients with the disease have been developed.
- Clinical improvement in active lupus nephritis has been obtained with the use of methylprednisolone and prednisone.
- Similarities have been discovered between Lyme disease in children and the joint involvement of classical rheumatoid arthritis.
- Discovery of enzyme variants in patients with gout has provided a better understanding of urate metabolism and the development of the disorder.

Pathways of Research Progress

Rheumatoid arthritis. Rheumatoid arthritis is a chronic inflammatory disease, affecting both small and large joints, that causes pain, weakness, fatigue, immobility, and deformity. Rheumatoid arthritis runs an erratic course characterized by periods of activity and remission, although it is basically a chronic disease that often may be progressive. Treatment remains largely nonspecific, as the cause of rheumatoid arthritis is not yet known. Improved methods of diagnosis, a new generation of modern drugs, and more effective methods of physical therapy now make it possible to keep most patients productive and comfortable and able to avoid many of the crippling effects of the disease.

Many NIADDK studies in rheumatoid arthritis are aimed at finding the exact origin of the disease process. For example, investigators are attempting to identify the primary event that precipitates rheumatoid arthritis by determining factors that regulate the synthesis, activation, and action of collagenase, an enzyme believed to destroy the protein collagen in cartilaginous tissue and joint linings. One promising development is the observation that collagenase is released in the joint as a latent enzyme, which can be activated by a variety of factors. Moreover, researchers have found that scavenging white blood cells (lymphocytes) are not exclusively responsible for all pathologic changes in rheumatoid arthritis. In fact, a "synovial cell," found at the junction of cartilage and granulation tissue, appears to promote progressive destruction through release of protein-degrading enzymes.

During the past few years investigations have also given strong support to the belief that rheumatoid arthritis can be attributed to an autoimmune reaction in which the body reacts to proteins originating within the body's own tissues. Such immune processes may be triggered by viral or bacterial agents, a process that could conceivably be prevented or counteracted once a viral or bacterial infection is established as the initial causative factor. Investigators have produced a form of arthritis in pigs that resembles human rheumatoid arthritis, by injecting them with mycoplasma organisms (organisms sharing characteristics of bacteria and viruses). Subsequent studies have shown significant evidence suggesting continual antibody production in the arthritic joints, even though the original causative organisms were no longer active. Various other infectious agents have been found in close association with rheumatoid arthritis, but none as yet has been shown to be an important direct or indirect cause of this disorder in humans. A rheumatoid arthritis-like disease has also been established in mice through an initial injection of tissue from human patients with rheumatoid arthritis. The mice thereafter transmit the disease from generation to generation without further inoculations, indicating that there may be some transmissible factor (such as a filtrable virus) in human rheumatoid tissue.

Scientists are also continuing to study the activity of prostaglandins (compounds which may cause or stimulate inflammatory changes in tissues) produced by a loose layer of connective tissue (synovial membrane) lining the joint cavity. Since prostaglandins are believed to modulate the inflammation of rheumatoid arthritis, investigators are exploring the possibility that these compounds inhibit the formation of new cartilage that could replace the cartilage destroyed by protein-degrading enzymes. Study findings suggest that prostaglandins present in human rheumatoid joint fluid significantly inhibit the metabolism of animal cartilage in culture. The precise role of prostaglandins in the cartilage destruction experienced by rheumatoid arthritis patients still remains uncertain. However, these and similar studies are contributing to a better understanding of cartilage metabolism and its relationship to the onset and progression of the disease.

Although the cause of rheumatoid arthritis is not known, scores of beneficial drugs have been evaluated clinically and some have been found useful in ameliorating the symptoms of the disease. The drugs range from new forms of time-proven salicylates, such as aspirin, to several types of potent corticosteroids and nonsteroidal anti-inflammatory drugs, some of which have also proved useful in treating osteoarthritis. Similar improvement of symptoms has been obtained with the use of gold salt therapy, D-penicillamine, and immunosuppressive drugs (such as cyclophosphamide and azathioprine). Rigorous basic science investigations into all aspects of this disease from its etiology to its effective clinical management are continuing in an effort to alleviate pain and disability for millions of sufferers.

Juvenile arthritis. Although arthritis is commonly viewed as a condition affecting elderly adults, thousands of children have this extremely painful disease. The most common form in children is juvenile rheumatoid arthritis. Extensive research now indicates, however, that this disease category includes several distinct clinical entities, which differ according to the extent and severity of joint involvement and the presence of organ dysfunction. In one particular population of juvenile rheumatoid arthritis patients, there is evidence of an inherited predisposition to the disease in association with a specific human leukocyte antigen (HLA, a tissue marker). However, this group of diseases is more appropriately termed juvenile chronic arthritis, as not all forms are rheumatoid in nature.

In other immunologic studies, a "hidden" rheumatoid factor in certain juvenile arthritis patients has been found through use of a highly sensitive laboratory test (complement-fixing hemolytic assay). Researchers determined that serum samples from over half of the patients studied contained the hidden factor, despite the fact that an initial, standard latex fixation technique yielded negative results. Thus, use of the more sophisticated assay method may lead to better definition of juvenile arthritis, together with greater insight into disease activity.

Early diagnosis and treatment, coupled with patient acceptance of therapy, are vital to the proper clinical management of juvenile arthritis and the prevention of serious complications. Highly individualized therapeutic regimens may limit attacks of arthritis and associated deformity, but patient, family, physician, and community programs on the optimal care of juvenile arthritis are equally essential adjuncts to basic biomedical research efforts.

Osteoarthritis. Over 16 million Americans are affected by osteoarthritis (degenerative joint disease), the most common form of arthritis. The disease is characterized by cartilage destruction and bony overgrowth in joints, especially major weight-bearing joints such as hips and knees. The disease is generally noninflammatory, unlike rheumatoid arthritis, and although it can occur at any age, it is more common in the elderly and develops progressively with advancing age.

One particularly promising research approach to osteoarthritis is the study of mechanical factors in joint destruction. With support from NIADDK, researchers have devised a microtransducer and an ultrasonic scanner for comparing the distribution of hip joint pressure with the detailed thickness distribution of weight-bearing cartilage that sheaths the human hip socket. Initial findings suggest that congenital or trauma-induced abnormalities—a common feature of osteoarthritis—will cause irregularly distributed stress concentrations in the cartilage layer that is so important to proper joint function. These techniques are enabling researchers to collect more accurate data concerning friction, wear, and mechanical behavior of cartilage and to understand the relationship of these events to degenerative joint disease.

Using a well-established surgical model for inducing traumatic osteoarthritis in animals, investigators have demonstrated that mechanical stability of weight-bearing joints, such as the knee, is important to the maintenance of the integrity of the cartilage in that joint. In this model, researchers have observed mechanical alterations in knee joints within 24 hours of surgery, 2 months before microscopically discernible changes were detected. By the end of 6 months, the joint evidenced progressive destruction, including surface irregularities and other gross osteoarthritic changes. Since mechanical alterations were seen much earlier than chemical or tissue changes, it would appear that under certain conditions, changes in the structure and function of joint biomaterials may be more sensitive indicators of cartilage dysfunction than are microscopy or chemical analyses of cells and tissues.

From a biochemical standpoint, researchers are studying the metabolism of cartilaginous tissue and changes in its metabolism, particularly those changes associated with age. They have determined the distribution and rates of synthesis of proteoglycans (protein and sugar-containing molecules) in normal and osteoarthritic joint cartilage, and their results strongly suggest that osteoarthritic cartilage cells have a metabolically hyperactive phase. In related research, other investigators have found that a lysozyme, an enzyme capable of degrading and dissolving tissues, may be responsible for the regulation of the state of aggregation of proteoglycans in the cartilage matrix. This finding is particularly significant as aggregated proteoglycans are subject to breakdown in osteoarthritic cartilage. It has also been found that collagen and proteoglycan synthesis and tissue-building activity within the cartilage matrix initially increase in arthritic tissue, but that this activity later decreases as the severity of the disease exceeds a critical point.

Armed with this knowledge on the natural progression of the disease, from both environmental and biochemical perspectives, it is hoped that appropriate measures can be developed to intervene in this process and halt its increasingly disabling consequences.

Systemic lupus erythematosus. SLE is a potentially fatal disease, primarily affecting women of childbearing age. The disease is systemic in that it attacks the entire body and its diverse organ systems, injuring connective tissue in the kidney, heart, and other vital organs. A surface feature of the disease is redness of the skin (erythematosus), particularly the appearance of a butterfly-like rash that spans the nose and cheeks and is often sensitive to light. Additional manifestations of SLE include arthritis, fever, pleurisy, pneumonia, blood abnormalities, heart disease, kidney disease (lupus nephritis), which causes the death of many patients with SLE, and central nervous system dysfunction evidenced by convulsions, psychoses, and other serious conditions. Arthritis is commonly the first manifestation of SLE and is the feature that most often brings the patient to medical attention.

Although researchers have yet to find an optimal treatment for SLE, the prognosis for patients has vastly improved in recent years. In 1955, the survival rate for SLE victims was only 50 percent 4 years after diagnosis. Now, more than 80 percent of SLE patients are alive 10 years after their disease has been identified. This increased survival may be due to a number of factors, including a greater awareness of the disease, better diagnostic methods, and development of more effective drug therapies. Nevertheless, many thousands of new cases of SLE are diagnosed each year, and much additional research is needed to pinpoint the underlying cause of the disease and to discover methods for preventing it or halting its progression.

There is accumulating evidence that SLE involves abnormalities of the immune system, and much of the Institute's current work in this area is oriented toward understanding the roles of antigens and antibodies in the disease process. For example, researchers are probing possible relationships between sex hormones, the thymus gland, and abnormal antibody production in SLE. Using an animal model, they have demonstrated that male hormones (androgens) and female hormones (estrogens) can have significant and opposite effects on the course of this apparently autoimmune disease. Results indicate that androgens suppress and estrogens enhance the disease process. The influence of sex

hormones is of considerable interest since it may help to explain the preponderance of women among SLE victims. Research teams are continuing to search for mechanisms whereby sex hormones exert their apparent influence on the immune system, and to test the therapeutic effectiveness of androgen administration on mice with established SLE.

Other researchers are investigating the role of immune complexes (fixed combinations of antigens with their specific, counterpart antibodies) in SLE-associated nephritis. Research indicates that immune complexes are not properly cleared from the blood of SLE patients and that the deposit of such complexes in the kidney, heart, and other sites is related to subsequent organ dysfunction and failure. Researchers are therefore injecting mice with various doses of soluble immune complexes in order to study the clearance mechanism through the reticuloendothelial system. Recent studies indicate that larger complexes, as well as complexes prepared with reduced and alkylated antibodies, persist longer in the circulation. Moreover, administration of cortisone before and during the experiment resulted in a greater quantity of complexes remaining in circulation, as well as prolonged clearance rates of larger complexes. Future studies will test various hypotheses that might explain these findings and thereby provide insight into the cause of renal failure in SLE patients.

In addition to searching for immunologic or environmental clues to the cause of SLE, NIADDK scientists are investigating different modes of managing the disease. Since a special breed of New Zealand mouse ("NZB") naturally develops SLE-like symptoms, this strain continues to be useful for the testing of experimental drugs. Ribavirin, a broad-spectrum antiviral agent, has been tested in NZB mice and appears to be an effective preventive and therapeutic approach to the disease. Since no toxicity was observed, these findings may help pave the way for future trials of Ribavirin in SLE patients. In humans, intermittent intravenous cyclophosphamide (an immune reaction suppressant) or a combined program of triple immunosuppressive drug therapy (prednisone together with low oral doses of cyclophosphamide and azathioprine), appears to be producing improved results. In fact, 80 to 90 percent of patients assigned to these regimens were stable or improved at a short followup interval. Patients admitted to these studies since 1973 continue to be followed with batteries of kidney function tests, urinalyses, and kidney biopsies, where possible, contributing to a more precise classification of SLE renal inflammation and nephritis and estimates of its prognosis. These data are extremely valuable since kidney failure is the major cause of death in SLE. Clearly the long-term, controlled results emerging from these studies will serve as an important clinical reference for treatment of SLE, and will help to advance the development of safer, more effective drug therapies.

Lyme arthritis. In 1976, NIADDK-supported researchers began to investigate the appearance of a strange new form of arthritis within the adjacent Connecticut townships of Lyme, Old Lyme, and East Haddam. After careful study, the scientists hypothesized and later traced Lyme arthritis to a tick bite. A slowly spreading skin lesion appeared to be the earliest manifestation of the disorder after the bite. Research also disclosed that the disease was found predominantly on the east side of the Connecticut River, where prevalence of a suspect tick species coincided with the distribution of Lyme arthritis cases. Interestingly, the disease is not restricted to the Lyme area, as cases have been reported in several other states, but this infectious type of arthritis has retained the popular name "Lyme" arthritis.

Research teams have examined hundreds of Lyme arthritis patients in an attempt to define the natural history of the disease and uncover additional clues to its origin. They have observed that headache, fever, and stiff neck often follow the appearance of the skin lesion from the tick bite and that, although these early symptoms may fade away, they are replaced by joint abnormalities (similar to classical rheumatoid arthritis), cardiac abnormalities (similar to the myocarditis seen with rheumatic fever), and neurologic abnormalities in certain patients. Clinical symptoms may vary greatly among patients, and erratic remissions and flareups—like those seen in rheumatoid arthritis—make it difficult to determine if the disease has run its course. Thus far, treatment of Lyme arthritis has focused on symptomatic approaches, such as aspirin ingestion and/or injections of corticosteroids in the knee, a frequent site of severe inflammation.

Since not all people who develop the skin lesion contract Lyme arthritis, scientists are exploring the possibility that a defective immune system predisposes some individuals to the systemic features of the disease. Recent studies in this regard have focused on a patient subgroup with neurologic diseases and/or arthritis persisting from 1 month to 1 year. In these patients, the prevalence of the tissue antigen DRw2 was significantly greater than that in normal individuals. This finding lends support to the theory that both a tick-transmitted infectious agent and an immunogenetic predisposition on the part of the host are necessary for the development of at least the more severe aspects of Lyme arthritis.

Investigators are now focusing their attention on efforts to control the illness, ascertainment of prognostic factors, treatment regimens, the long-term effects of the disease, and the development of an animal model of the disease. Finally, the possible roles and interrelationships of circulating immune complexes, lymphocyte dysfunction, blood coagulation abnormalities, and immunogenetic determinants of the disease will be explored.

Psoriatic arthritis. Psoriasis, a skin condition characterized by scaly red patches on surface areas of the body, can be associated with symptoms of arthritis and other systemic manifestations in about 10 percent of the cases. Although psoriatic arthritis resembles rheumatoid arthritis in some ways, it seems to be a separate

clinical entity requiring different therapeutic approaches. Thus, investigators have undertaken clinical trials on patients with psoriatic arthritis in an effort to define the characteristics of this disease and to evaluate different drug treatments. These investigators have found that several features distinguished psoriatic arthritis from other types of arthritis, i.e., a paucity of "rheumatoid factors" (substances frequently found in the blood of rheumatoid arthritis patients), a lack of symmetry in the joints involved, radiographic demonstration of joint involvement primarily in finger and toe bones, abnormal nail changes, a clustering of psoriasis and psoriatic arthritis in first-degree family members, and significant association with the tissue antigen (marker) HLA-B27. In addition, they observed that psoriatic arthritis patients treated with aspirin and hydroxychloroquine, an antimalarial drug, experienced a beneficial response in 75 percent of trials—without exacerbation of psoriasis. Patients receiving treatment with gold salts responded in 63 percent of the trials, while of those receiving nonsteroidal, anti-inflammatory agents, 55 percent displayed suppressed disease activity but not remission. These findings support the view that psoriatic arthritis is a distinct form of rheumatic disease and offer valuable comparative data on existing drug therapies.

Gout. Arthritis has often been regarded as a life sentence to pain, but recent discoveries have shown that some arthritic conditions once believed virtually hopeless can be very well controlled after an understanding of their basic mechanisms is achieved. Gout is a case in point. Formerly a disease only partially controllable and excruciatingly painful, replete with severe and dangerous complications, gout is now one of the most controllable afflictions in the arthritic group of diseases. Gout is a centuries-old disease, long believed to be a consequence of overindulgence in rich food and drink and, in general, the result of an extravagant lifestyle. However, within the last 30 years, NIADDK scientists and grantees have determined that the inherited overproduction and/or underexcretion of uric acid are the key flaws in body chemistry that are truly responsible for this painful disorder.

In this inherited metabolic disease, excessive quantities of uric acid, a substance normally elaborated in the body, are deposited in tissues and joint spaces. When uric acid crystals accumulate in joints of the feet and elsewhere, inflammation and severe pain result. Many years after onset of gout, localized chronic arthritis may appear. Moreover, kidney disease due to an accumulation of urates in the kidney and subsequent high blood pressure may develop if gout is not detected and treated in its early stages. Having elucidated the cause and mechanisms of this classically crippling disease, NIADDK-sponsored investigators pursued improved methods of diagnosis and highly effective new modes of drug therapy. This knowledge, derived from basic research investigations, has now made gout one of the best managed of serious disorders, and patients afflicted with it can lead normal and productive lives without fear of its painful attacks and serious long-term joint and kidney complications.

The tremendous improvement in the clinical management of gout in recent years has been made possible by advances in biomedical research largely supported by this Institute. NIADDK-supported scientists demonstrated that the well-known drug colchicine acted to interrupt gouty attacks by diminishing the metabolic activity of defensive white blood cells accumulating in the joints and reacting with precipitated urate crystals to produce inflammation and pain. Even more recently, newer drugs such as allopurinol and probenecid have been developed, which either effectively decrease the production of uric acid in the body or stimulate the excretion of uric acid in the urine and effectively lower a patient's uric acid level below the point at which urate deposits appear. Research into the development of effective, nontoxic uricosuric drugs with diuretic and antihypertensive properties continues, as well as work on the elucidation of the basic underlying defects in gout.

Program Accomplishments

Multipurpose Arthritis Centers. A central feature of both the National Arthritis Act of 1974 and the national Arthritis Plan is the concept of establishing and supporting Multipurpose Arthritis Centers (MACs) throughout the country. The purposes of the centers are to serve as major resources for generating new knowledge and disseminating information on the causes and control of arthritis and related musculoskeletal diseases and to demonstrate and promote the application of available knowledge for the treatment of arthritis patients. In order to accomplish those aims, the centers program is organized to provide for activities in three areas—research, professional and patient education, and community demonstration programs.

Each MAC is expected to possess a substantial base of ongoing basic and/or clinical biomedical research in areas related to the rheumatic diseases. These activities are not supported by the center grant funds, per se, but rather through traditional research grants given to individual research workers in the particular institution. Center funds are used, however, to support developmental and feasibility studies in rheumatology-related areas of biomedical research. These studies are an important feature of the MAC program in that they encourage investigators to explore interdisciplinary and highly innovative scientific approaches that may later form the basis of regular research grant applications.

Many exploratory or pilot research projects now under way could not have been started without the interaction of individuals brought together under the aegis and support of the arthritis centers grants. As the program has grown, increased support has been given to each center for innovative pilot or feasibility research projects that supplement the traditional investigator-initiated research grants of individual workers associated with each center. This research encompasses a wide

range of disciplines and interests from basic biomedical research to health services research.

In addition to the numerous basic research pilot and feasibility studies conducted at the centers, several MACs are also conducting clinical trials to determine the efficacy of newly developed anti-inflammatory drugs in the treatment of arthritis. Because of the large numbers of arthritis patients available for study on-site, the MACs provide an ideal setting for closely monitored, effective evaluation of the new treatment regimens prior to their dissemination and application in the general public.

Another important purpose of the Multipurpose Arthritis Centers continues to be served by their educational activities. Many ongoing projects are intended to improve rheumatic disease care at the level of the primary care physician through studies designed to identify and/or develop effective training approaches. Some of the professional education approaches being investigated at the centers include:

- The development of a computer-based system for clinical consultation by nonrheumatologist physicians in areas where this expertise is unavailable;
- Continuation of the Dial-Access System by which a toll-free long-distance telephone call can place a physician in touch with tape-recorded messages for medical consultation on arthritis problems; and
- The utilization of trained patient-instructors to provide training to medical students in the correct methods of physical examination of joints and clinical diagnosis of arthritis-related problems.

In addition to the basic research and training offered by MACs, selected centers also offer special programs in pediatric rheumatology, community projects studying the social and economic impacts of arthritis, and model demonstrations of care in locations outside the center. These programs seek to increase the general public's awareness of the problems of arthritis as well as provide a high level of quality care for all aspects of the disease.

For all center activities—basic research, clinical care training, clinical trials, professional education, community projects, and demonstration projects—a special emphasis of the NIADDK program management is to foster intercenter activity, collaboration, and information exchange. This is done through the sponsorship of annual meetings of the MAC directors, compilation of a directory of center personnel, production of an index of audiovisual materials produced by the centers, and the sharing of educational facilities. This highly coordinated approach to research and clinical care in arthritis assures that the highest possible level of care is made available in a timely and effective manner for the benefit of the greatest number of patients.

Arthritis Information Clearinghouse. The Arthritis Information Clearinghouse, established in 1978 by NIADDK, continues to develop along the lines recommended by the National Commission on Arthritis and Related Musculoskeletal Diseases' **Arthritis Plan**, which called for the collecting, screening, storing, and dissemination of information about educational materials and programs on the rheumatic diseases. The clearinghouse serves as a repository or "broker" for a nationwide flow of arthritis information designed to help health professionals and educators in their interaction with patients, their families, and the public.

In addition, the clearinghouse reviews, abstracts, indexes, and analyzes bibliographic and audiovisual materials and maintains a retrievable data base. Upon request by professional user groups, the clearinghouse selectively searches its data base and other bibliographic sources for relevant citations, abstracts, and information on the availability of materials.

The clearinghouse is interested in collecting information on community and institutional patient education and in-service training programs related to arthritis. Since many of the Multipurpose Arthritis Centers are emphasizing team care and developing programs and resources to implement education programs, the clearinghouse will catalog MAC efforts in this area and incorporate that information into its data base.

As the bibliographic information services become fully developed and operational, future efforts will be directed toward determining the effectiveness of the clearinghouse program and improving its utility for its wide range of user audiences.

Arthritis Epidemiology and Data Systems. The Arthritis Epidemiology and Data Systems program serves as the administrative focus of efforts to encourage and support epidemiologic research in the field of arthritis and related musculoskeletal diseases.

It has been generally held that an important interplay exists between biomedical research and epidemiology, and that the latter area, underexploited in recent years, may provide vital leads in poorly understood etiologic mechanisms of several rheumatic diseases.

The need for epidemiologic studies of the rheumatic diseases is viewed now as particularly compelling because the results of biomedical research suggest that susceptibility to several of these diseases may be linked to measurable genetic characteristics and that microorganisms or viruses may be important in their pathogenesis. Such studies of disease susceptibility have been hampered by a shortage of trained arthritis epidemiologists.

In an effort to foster renewed interest in this area and attract researchers to epidemiologic studies of the rheumatic diseases, NIADDK sponsored the Arthritis Epidemiology Conference in the fall of 1980. At this conference, an interdisciplinary, international group of rheumatologists and epidemiologists convened to review the current state of epidemiologic knowledge of the rheumatic diseases, define gaps in present knowledge, identify research opportunities, propose research strategies, and determine required resources. As a result of the conference, four publications are in preparation. Both the conference and the publications were designed

to increase awareness of research opportunities in both the epidemiologic and rheumatologic communities.

MUSCULOSKELETAL DISEASES

More than 40 million people in the United States suffer from bone and joint diseases, fractures, and disorders of the tendons and ligaments. The resulting loss to the national economy, in terms of disability and decreased productivity, is enormous.

The musculoskeletal diseases program at NIADDK encompasses a broad range of research areas from rare congenital disorders to osteoporosis and bone transplantation. The program's activities are organized in four broad scientific areas:

- Bone properties, growth, and metabolism;
- Bone diseases, injuries, and repair;
- Joint diseases, traumatic injury, and treatment; and
- Skeletal support structures and functions—tendons, ligaments, locomotion, back disorders, and exercise pathophysiology.

The rapid rate of technological developments in joint replacement has been particularly dramatic. The development and successful use of artificial hip implants almost two decades ago has paved the way for the development of many other joint prostheses, the use of which has restored mobility and freedom from pain to literally hundreds of thousands of individuals. As the state of the art in joint replacement has progressed, new "bone cementing" techniques have been developed to assure better fixation of implants to adjacent natural bone, and new biocompatible materials capable of withstanding long-term wear have been introduced. These advances have permitted the use of artificial implants in progressively younger individuals (who would use these implants more vigorously and for longer lifespans) with the hope of long-term benefit.

NIADDK also supports substantial research on osteoporosis—a widespread disease of particular significance in older women. Basic research and epidemiological studies of the natural history of this disease as well as clinical trials of new therapeutic agents are going on in an effort to elucidate the underlying causes and to provide a firm foundation for future therapy to prevent and eliminate the resultant disability.

These are just two examples of many ongoing studies in orthopedic and bone diseases supported by NIADDK. The return on this research investment is far-reaching, since discoveries about one disease may help to advance our knowledge about and our ability to treat other musculoskeletal disorders and related arthritic conditions.

Highlights of Recent Advances

The following presents highlights of recent advances in the rapidly evolving field of musculoskeletal disease research that are leading to dramatically improved methods of therapeutic intervention in a variety of diseases and disorders.

- A vitamin K-dependent amino acid has been shown to be the precursor for a protein component in bone, and the isolation and characterization of bone growth factors is helping to elucidate the bone metabolism cycle
- Recent advances in the application of direct electric current or electromagnetic stimulation have been successful in promoting healing in the vast majority of nonunion bone fractures.
- Recent improvements in wear- and corrosion-resistant biomaterials and pressurized application of bone cement have yielded dramatic improvements in the postoperative success rates for artificial joint implantation

Pathways of Research Progress

Paget's disease. In Paget's disease, a defect apparently exists in the continuous process by which existing bone is replaced by new bone. Excessive destruction of old bone occurs, and cells begin to rebuild bone tissue in a hyperactive fashion. Unfortunately, the newly formed bone tends to be fragile, structurally abnormal, and painful. Previously, little could be done to help patients with Paget's disease except to prescribe pain-killing agents. During recent years, however, the therapeutic value of the hormone calcitonin has been discovered.

Over the past decade scientists have successfully isolated, characterized, and synthesized calcitonin, which is naturally produced by the thyroid gland. Victims of Paget's disease are now experiencing restored mobility, as well as remarkable freedom from pain, through the self-administration of calcitonin injections. Synthetic calcitonin derived from salmon sources has been found to be clinically effective and relatively easy to obtain and is also currently used in the therapy of Paget's disease. NIADDK has long supported work in this area, and is continuing to fund studies of the use of calcitonin in Paget's disease as well as studies to define more fully the role of the other hormones involved in mineral and bone metabolism.

Since curative therapies for Paget's disease patients are not yet available, the search also continues for new knowledge upon which methods of prevention or cure can be based. For example, upon examining bone biopsies obtained at surgery from Paget's disease patients, investigators have recently discovered virus-like structures in the cell nuclei of biopsy samples. These structures are very similar to those found in the brains of children who have died from measles and subacute

sclerosing panencephalitis—a disease in which a latent, slow-acting virus infects the central nervous system. Since patients with Paget's disease frequently have antibodies that react with several types of viruses, some researchers think that the disease may be caused by a persistent viral infection that begins in childhood and becomes clinically active only many years later. If this is the case, improvements in patient treatments and, perhaps, even prevention of the disease through immunizing vaccines may be possible.

Osteoporosis. Osteoporosis is a disease characterized by reduced bone mass. It affects an estimated 10 million to 15 million people in the United States, usually older individuals, particularly women past menopause. Osteoporosis is essentially a depletion of minerals and proteins resulting in less dense bone. Bone pain is not a common symptom of the disease, but susceptibility to bone fracture (especially fractures of the hip and vertebrae) is of major significance. To elucidate factors related to development of postmenopausal osteoporosis, investigators have undertaken a 20-year longitudinal study of calcium and bone metabolism in normal volunteers. Two forms of therapy are being evaluated for treating development of osteoporosis in this study group—estrogen/androgen administration and calcium supplementation. In addition, assessment of physical activity and locomotor stability, as well as pathologic hormone profiles, will be related to the extent of the disease. This study should provide a clearer picture of the natural history of postmenopausal osteoporosis and insight into the disease process.

In another study related to osteoporosis, a thousand individuals who were initially studied 20 years ago (by means of X-rays to assess levels of skeletal maturation and bone mineral content) will be reevaluated. This followup should provide useful comparative data for understanding bone changes during the aging process. Moreover, information concerning the role of lifestyle, exercise, and nutrition in the development of osteoporosis will be correlated with radiographic findings.

Presently, little can be done for the patient with osteoporosis to prevent the frequent bone fractures that are a consequence of this disease; however, researchers have performed clinical investigations with the therapeutic agent sodium fluoride in combination with calcium and vitamin D. Preliminary results showed a reduction in symptoms during a 16-month study period, and evaluations of the safety and efficacy of this mode of treatment are continuing, as are correlative studies on the basic biological metabolism of fluoride by the body.

The precise underlying factors preceding the development of osteoporosis are still not known; however, recently initiated studies are searching for a factor that may be responsible for maintaining the balance between bone formation and bone resorption. Such an agent may be the controlling substance whose function is altered in osteoporotic patients; and, if it can be identified, correction of its altered regulatory function may provide a firmer foundation for therapeutic intervention.

Osteogenesis imperfecta. One of the most serious of the inherited connective tissue diseases is osteogenesis imperfecta (OI), a disease that may affect bone, eye tissue, inner ear, teeth, and/or skin. Although there are many forms of the disease with varying degrees of severity, a typical form involves frequent bone fractures due to bone fragility and often results in severe deformities of the body. An estimated 20,000 to 30,000 Americans (mostly children) are afflicted with this "brittle bone" disease, and it is estimated that OI affects 1 in every 40,000 to 50,000 infants born each year.

Since existing therapies for OI are largely ineffective, researchers continue to focus on fundamental studies to obtain new knowledge from which better medical interventions can emerge. For example, scientists are attempting to determine the biochemical defect in OI, which appears to involve production of abnormal collagen. Although the quantity of collagen in OI patients seems to be adequate, the specific type of collagen and the distribution of this connective tissue protein are somehow altered.

Scientists are exploring the hypothesis that structural mutations in the procollagen molecule (the precursor of collagen) may alter its biological function in patients with certain forms of osteogenesis imperfecta and Ehlers-Danlos syndrome (EDS). Using cultured skin cells (fibroblasts) from OI and EDS patients, scientists are attempting to determine whether defects have occurred in the genetic transcription and translation of collagen, or whether a deficiency exists in one of the many enzymes involved in the processing steps required for collagen biosynthesis. If an enzymatic deficiency is identified, the next step will be to determine whether these patients synthesize a less active or unstable form of the enzyme.

Joint replacement. The development of artificial hip joint implants is perhaps the most exciting orthopedic research advance of the last two decades. Moreover, this achievement is now serving as a model for the design of implantable knee, elbow, shoulder, and other joint prostheses, as research rapidly expands the science base from which these new orthopedic discoveries can emerge.

NIADDK is supporting multiple research projects on the design and implantation of joint prostheses, as well as on the improvement of biomaterial components, making them more resistant to wear and corrosion. Implant fixation presents the most serious technical problem in joint replacement, as prostheses in place for many years tend to loosen at points where they were attached with "bone cement" to adjacent natural bone. Researchers are currently testing the theory that failure at the bone cement interface may relate to the leaching of chemicals out of the implant. This can also lead to poor vascularization and invite the problems of late infection that have been experienced by certain patients. To test this theory, researchers have developed an animal model of prosthesis loosening, thus permitting them to study this phenomenon chemically, pathologically, and structurally. Researchers are also evaluating results

obtained when variations are made in cement insertion techniques, cement fluidity, cleaning and drying of the joint cavity, and other aspects of implantation.

In additional work on fixation methods, investigators are studying growth of surrounding living bone into implants as a means of prosthesis attachment. In these studies it has been shown that electrical stimulation via external power packs or piezoelectric implants can enhance bone growth into porous implants and can strengthen the implanting interface in experimental animals. These approaches may help to identify methods for limiting implant failures at the bone interface, the major long-term problem in human joint replacement.

Bone fracture and healing. NIADDK research support has been instrumental in the development of major new approaches to the clinical management of fractures resulting from both trauma and pathological lesions. One such advance, electrical stimulation of bone formation, is based upon the production of an electrical current that flows into the bone from an external energy source. It has been demonstrated that a 2 microampere to 10 microampere direct current will improve healing of fractures and congenital lesions involving local nonunion that previously had not responded to conventional therapy. Research on this technique, as well as clinical experience, has shown both short-term safety and efficacy when electrical current is used within well-defined guidelines for treating nonunion of fractures, failure in fusion surgery, and congenital pseudoarthrosis (characterized by development of a "false joint" in a weight-bearing long bone). The Food and Drug Administration has recently approved the use of three electrical stimulation devices for limited use in patients with these conditions.

NIADDK-supported scientists have been working with two types of electric stimulation devices—direct current and electromagnetic—to determine their mechanism of action, the optimum pulse rate of electric current for different conditions, and whether the treatment produces any long-term side effects.

Ultrastructural studies have shown an initial invasion of polymorphic (nonspecialized) cells after electrical stimulation of a fracture site, signifying the beginning of the healing process, as well as calcification preceding the production of specialized osteoblasts (bone-making cells)—both normal events in bone repair. Other results showed a decrease in the partial pressures of carbon dioxide and oxygen near the device where the healing is being stimulated. This reduction in the presence of oxygen has previously been associated with favoring bone production and may help explain some of the beneficial effects of the electrical stimulation. Electrical stimulation of bone is also being investigated for possible use in the local treatment of osteoporosis and osteogenesis imperfecta.

SKIN DISEASES

Diseases of the skin, while not usually producing major physical disability, can exact a high toll in terms of the resultant psychologically damaging, unattractive appearance and disfigurement. A formal analysis of research needs and priorities in dermatology, completed for NIADDK in 1979, clearly established dermatological disease as a major cause of illness and loss of gainful employment. In addition, costs for hospital care, professional services, topical preparations, and lost productivity place a heavy burden on the Nation's economy.

Diseases of the skin concern almost all of us at some time during our lives, and NIADDK supports research in all aspects of these disorders. This research can have far-reaching consequences beyond improvement of psychological well-being and physical appearance in that some skin diseases, such as psoriasis, are frequently found in association with arthritis, while others may involve multiple organ systems or may be indicative of abnormal immunologic defenses.

The goal of NIADDK's skin diseases program is to provide the means for preventing, treating, and curing a wide range of skin diseases and their complications. To that end, the program supports clinical and laboratory research on both normal and diseased skin to obtain a better understanding of disease cause and progression. NIADDK has taken the lead in reviewing research problems in skin biology and skin diseases and in analyzing the needs and priorities for future dermatological research. In coordination and collaboration with other Federal agencies, NIADDK also supports the Interagency Dermatology Working Group, whose efforts are directed at identifying new research opportunities in

Highlights of Recent Advances

The following are brief highlights of some of the more recent advances in basic, applied, and clinical research supported by NIADDK directed toward the prevention and treatment of skin diseases.

- The anticonvulsant drug diphenylhydantoin has been shown to reduce significantly the incapacitating blistering of the debilitating and, to date, incurable skin disease epidermolysis bullosa
- Small daily doses of the drug 13 **cis**-retinoic acid (13-**cis**-RA) have been shown to inhibit sebaceous gland activity, thus leading to dramatic improvement in disfiguring acne refractory to any other treatment
- The increased numbers of white blood cells found in the circulation of patients with psoriasis have also been found to behave differently from normal white blood cells, supporting the hypothesis that psoriasis is a systemic disease and that certain types of white blood cells contribute to the generation of psoriatic skin lesions.

dermatology and at increasing the awareness of scientific investigators with regard to the need for more research and manpower to address these issues.

In recent years, these combined efforts on the part of NIADDK have ushered in significant therapeutic advances in the treatment of skin diseases—systemic cytotoxic and retinoid agents as well as psoralen ultraviolet light therapy (PUVA) for psoriasis, topical steroids for eczematous and immunologic skin diseases, and topical retinoids and systemic antimicrobials for acne. In large measure, all of these diseases are treatable, but at present they are neither curable nor preventable. Toward this end, basic research on the cause and progression of skin diseases must be continued and intensified.

Pathways of Research Progress

Psoriasis. Psoriasis is a scaling disease of the skin and produces chronic recurrent lesions that are often emotionally and physically debilitating to the patient. Frequently, lifelong expensive treatment is required. Recent estimates indicate that 1 million to 3 million individuals suffer with psoriasis and that between 150,000 and 260,000 new cases of psoriasis are diagnosed annually. Results of a recent study indicated that, of all skin diseases, psoriasis had the highest number of repeat visits per year to a physician's office, and that the average expenditure per year for physicians' fees, medications, hospitalization, and loss of work days was $5,456 per patient, much higher than previously estimated.

The etiology of psoriasis is unknown; it is neither preventable nor curable at the present time. There are a few drugs, which can be taken internally or applied locally to the skin, that are capable of partially or totally eliminating the lesions of psoriasis. Topical therapy, mainly the use of corticosteroids, has been the mainstay of psoriasis treatment, with less than satisfactory results. A new treatment, psoralen ultraviolet light therapy, combines an oral medication with local exposure of the skin to ultraviolet light and has been found to be very effective in controlling the lesions of psoriasis. Since it is an outpatient treatment, PUVA offers an alternative to expensive hospitalization for severe cases of psoriasis. Cooperative studies show outpatients could be treated for a year with photochemotherapy for one-third the cost of hospitalization for those patients. Ongoing clinical studies supported by NIADDK are continuing to examine the possible long-term side effects of this promising new clinical approach to the treatment of psoriasis. Recently it was shown that retinoids and PUVA can be used together and that, with use of this combination, the number of PUVA treatments required to clear the skin can be reduced by one-half.

Although some enzymes (proteinases) found in the skin of psoriatic patients may not play a role in the treatment of psoriasis, it has been determined that they may be directly associated with cellular proliferation. Recent data strongly suggest that proteinases should be investigated further to determine whether they play a role in the development of psoriasis. Basic studies on the regulatory role of these enzymes and other growth factors on skin proliferation may provide the basis for the development of new therapeutic approaches in the future.

Acne. Acne vulgaris, the most common disease of the skin, in various degrees affects more than 80 percent of the population, usually during the second and third decades of life. This normally difficult transition period is further aggravated by the additional burden of a disease that is at the least unattractive, and at the worst, severely disfiguring. The impact of both mild and severe forms of acne upon the quality of life can be significant in terms of emotional distress, withdrawal, and a variety of desperate attempts at self-treatment.

Although the majority of patients benefit from treatment with topical retinoic acid, systemic and topical antibiotics, benzoyl peroxide, or estrogens, a small number of severe cases are characterized by cysts and pustular nodules resistant to these conventional therapies. The persistent lesions in such cases account for unsightly appearance and scars, and result in considerable suffering. A therapeutic solution appears to reside in 13-**cis**-retinoic acid, a new analogue of a naturally occurring vitamin A derivative that is a member of a class of synthetic retinoids originally developed for prevention of chemically induced cancer. In a recent clinical study supported by NIADDK, it was observed that the oral use of 13-**cis**-RA dramatically eliminated most nodules and cysts in treatment-resistant cases. Prolonged remissions lasting up to 20 months after the cessation of treatment were observed. Such results, considered together with the evidence of relatively low toxicity, render this drug more effective and safer than some conventional therapies for severe acne.

Vitiligo. The brown pigment that gives human skin its distinctive hue is a protein material called melanin. Melanin is manufactured within specialized skin cells called melanocytes, and during the pigmentation process melanin granules are transferred from the pigment cells to adjacent epidermal cells. Various skin colors are the result of different amounts of melanin within the epidermal cells and racial variations of skin color correlate with the amount of melanin produced and transferred to these epidermal cells.

Vitiligo is a common disorder of the pigment system in which pigment cells of the epidermis disappear, thereby causing irregular, smooth white patches on the skin. Most commonly, the disease leaves large white patches around the eyes, nose, mouth, nipples, genitalia, and hands. In persons with light-colored skin, the disease may not be apparent, but for most dark-skinned individuals or those with widespread areas of depigmentation, especially on exposed portions of the body, the cosmetic effects can be psychologically devastating.

Vitiligo most commonly occurs as an inherited disorder not often associated with impaired health, although it may on occasion be accompanied by serious

physical symptoms or may occur as a secondary manifestation of a variety of systemic diseases. Over half of the patients with vitiligo also have abnormalities in the pigment system of their eyes, which can result in decreased night vision and sometimes produce significant disturbance in all vision. Twenty to thirty percent of patients who have melanoma, a potentially fatal cancer of pigment-producing cells, also have vitiligo. In total, an estimated 1 million people in the United States have vitiligo.

The cause of vitiligo is unknown. Treatment is enormously expensive and time-consuming and produces only modest and often disappointing results. NIADDK supports a significant program of research, research training, and public and professional education in vitiligo. To stimulate such research, NIADDK sponsored a workshop in 1978 on melanocyte-related diseases. Following this workshop, the Institute awarded a large grant to a consortium of universities to undertake an extensive examination of all aspects of this disease. Through this grant, a pigment cell clinic is in operation and attended by over 350 patients with vitiligo. Through verbal and clinical examination of these individuals, new information on natural progress and clinical aspects of the disease is being collected. This clinic is also working to find ways of delivering improved care to patients with vitiligo.

Bullous skin disease. Major research within the skin diseases program has been concerned with supporting structures of the skin, namely the connective tissue. An interesting overlap between the study of connective tissue and bullous diseases of the skin has become more evident recently with increased attention to the disease epidermolysis bullosa. The bullous skin diseases are a group characterized by blistering bullae or papules arising from inflamed or noninflamed skin that, upon rupture, leave large weeping, denuded areas of skin. These diseases are therefore not only disfiguring, but also quite painful.

In the current fiscal year, Institute staff and collaborating investigators in the field have planned a state-of-the-art workshop on epidermolysis bullosa and other blistering diseases of the skin. Such a workshop seems timely, as it has recently been reported that increased human skin collagenase may be implicated in the pathogenesis of blister formation in recessive dystrophic epidermolysis bullosa. Recently investigators have also tested the effects of an anticonvulsant drug, diphenylhydantoin, on the action of collagenase in this disease. Although the drug did not inhibit collagenase activity directly, it appeared to produce a significant decrease in collagenase activity, accompanied by a favorable clinical response, as exemplified by a marked decrease in the incidence of blistering in the patients tested.

In addition to basic research on epidermolysis bullosa, the program staff has recently initiated interaction and cooperation between officers of the newly formed Dystrophic Epidermolysis Bullosa Research Association (DEBRA) and scientists studying blistering diseases of the skin; NIADDK will be cooperating with DEBRA in providing information to patients and scientists on resources available for the treatment of this disfiguring disease.

Ichthyosis and congenital disorders of keratinization. Ichthyosis and congenital disorders of keratinization (formation of the scaly protein that constitutes skin, hair, and nails) affect approximately 1 percent of the population. Diseases within these categories include several types of ichthyosis (excessive production of keratin), epidermolytic hyperkeratosis, pityriasis rubra pilaris, and Darier's disease. As with other genetic diseases, experience suggests that there is a discrete molecular defect peculiar to each of these disease states and only increased knowledge of the specific molecular flaw will enable researchers to develop cures.

There have been a variety of biophysical and biochemical studies performed on the skin and on the general body metabolism of patients with ichthyosis. Biophysical studies have suggested that in some forms of ichthyosis an abnormal structural protein is made in the epidermis; in other forms of ichthyosis, both microscopic and biophysical studies have suggested that maturation of the epidermis is incomplete.

For decades, topical agents such as glycerin have been used to treat ichthyosis. Recently, new agents such as hydroxy acids, vitamin A acid, and propylene glycol, which are suitable for some forms of ichthyosis, have been developed. In addition, systemic vitamin A analogues and antimetabolites are also being found to be useful in treating some forms of this disease. Clinical research in disorders of keratinization continues to seek new topical therapy for these diseases, concentrating on compounds that will control the abnormal epidermal proliferation.

Eczematous and immunologic skin diseases. Eczematous and immunologic skin diseases are among the most common clinical afflictions. They have a great physical and economic impact on society and at times they can be devastating.

Atopic dermatitis is a chronic inflammatory skin disease that occurs most frequently in persons with a personal or family history of other allergic problems, such as asthma or hayfever. It occurs in 2 to 3 percent of children 1 to 5 years old, and 120,000 to 150,000 new cases occur each year. Followup surveys of 15 to 20 years showed persistence of atopic dermatitis in approximately 60 percent of these cases with the most severely affected patients being more likely to retain the disease. The hallmark of atopic dermatitis is intense itching which induces scratching that worsens, if not causes, the skin lesions. Disease severity ranges from dry, itching, easily irritated skin to total body weeping and redness. Exacerbations interfere with sleep, work, and social relationships and chronic involvement may cause considerable occupational and social disability. It is estimated that 25 to 50 percent of all occupational hand eczema (leading occupational disease) occurs in atopic (allergic) individuals.

The cause of atopic dermatitis is not known, and it cannot be prevented or cured. The only effective medications at present are topical steroids which, unfortunately, cause many undesirable side effects with continued daily use, and there are no satisfactory systemic medications. Complications of atopic dermatitis include severe viral or bacterial infection, which can be fatal in infants; cataracts in many of those who have had severe atopic dermatitis for many years; generalized erythroderma, or extensive scaling dermatitis of the entire body, resulting from infections and prolonged use of corticosteroids; and food sensitivity, especially in infants, requiring careful food selection for those affected.

Our understanding of skin disease has greatly advanced during the past 15 years and much of this progress can be attributed to major advances in knowledge relating to basic immunologic mechanisms. It has become clear that the skin is a target for diverse assaults by the immune system. Patients with atopic dermatitis have a constellation of immunological defects—elevated serum IgE levels, depressed cell-mediated immunity, and reduced or abnormal leukocyte scavenging of foreign material. Institute grantees are currently trying to determine whether these immunologic abnormalities represent the primary defect or only a secondary response to inflammation. They are also attempting to demonstrate why many patients with atopic dermatitis display diminished reactivity to specific antigens. This deficiency may or may not be related to local skin factors or possibly to central immunologic defects, and in future work it will be important to determine whether the increased IgE production is regulated by specific T-cell subpopulations or by other controlling mechanisms.

DIABETES, ENDOCRINOLOGY, AND METABOLIC DISEASES

DIABETES

Diabetes mellitus has been diagnosed in over 5 million Americans and probably affects an additional 5 million. It is the fifth leading cause of death by disease in the United States, but the full toll of diabetes is considerably higher, as its vascular complications contribute heavily to the cardiovascular and cerebrovascular death statistics. In addition, many hours of productivity are lost to complications of the disease—retinopathy and blindness, kidney disease, cardiovascular problems, increased susceptibility to infection, and neuropathy. It is estimated that diabetics in the United States spend about $4 billion for medical care each year.

Diabetes is characterized by elevated blood sugar levels and various other metabolic and endocrine disturbances that affect the regulation of carbohydrate, protein, and fat metabolism, and by widespread, chronic, degenerative lesions affecting almost every tissue of the body—the so-called diabetic complications.

In general terms, diabetes can be divided into two clinical types with different prognoses, some differences in treatment, and causative mechanisms that are probably related but dissimilar. The two types are called insulin-dependent ("juvenile") diabetes; and noninsulin-dependent ("maturity-onset") diabetes. Insulin-dependent diabetes usually begins in early life—before age 40—and it is characterized by a rapid progression to a requirement for daily insulin injections. Unless insulin is provided for the condition, patients will develop ketoacidosis, a buildup of acids and ketone bodies in their tissues and fluids, with a fatal outcome. Insulin-dependent diabetics commonly experience greatly accelerated degeneration of blood vessels in many organs, which can lead to kidney failure, gangrene in the extremities, heart attacks, neuropathy, and blindness. Even with insulin treatments, the life expectancy of such patients is measurably shortened.

About 85 percent of all diabetics have the noninsulin-dependent form of the disease, which usually begins after age 40 and is characterized by a slower progression of the disease and its complications. Such patients usually do not develop ketoacidosis, they usually do not require insulin, and they usually can maintain relatively normal blood sugar levels by adherence to prescribed diets, control of body weight, and/or use of oral agents to lower blood sugar levels. However, noninsulin-dependent diabetics also have a decreased life expectancy because of a variety of chronic vascular and neurological complications.

It is thought that diabetes probably represents a heterogeneous group of diseases, and its cause or causes are not precisely known. Studies suggest the presence of a genetic component in both insulin-dependent and noninsulin-dependent diabetes, but the patterns of inheritance of the two types are clearly different and poorly understood. Other studies indicate that environmental factors, such as viral infections or obesity, interact with genetic susceptibility in both types of diabetes to heighten the risk of clinical expression of the characteristic symptoms of altered glucose metabolism.

The major aims of NIADDK's diabetes program are to define the disease fully in terms of its causes and many complications, and to find improved methods for the diagnosis, treatment, cure, and prevention of both the disease and its chronic complications. To achieve these goals, better methods must be established for detecting the disease as early as possible and for predicting the risk of occurrence in defined patient populations. Furthermore, the genetic, immunologic, and environmental causes of the disease and the factors that lead to its complications must be understood better so that rational methods of treatment and prevention can replace the present empirical approaches.

Although full resolution of the many clinical problems associated with diabetes and its complications must await further research, there is now reason to hope that its cure and prevention may one day be a

reality. This prevailing optimism is based on recent scientific advances that have resulted from the Institute's increased support of diabetes-related research.

The attack on diabetes includes basic and clinical research, bringing to bear all of the scientific disciplines. This broad-based, programmatic approach to diabetes research over the last several decades has produced advances in diagnosis and management that translate into improved life expectancy and improved quality of life for all diabetics.

Highlights of Recent Advances

The following briefly highlights some of the more significant recent advances in diabetes research.

- The importance of genetic, viral, and immunologic factors in the development of diabetes has been demonstrated.
- Significant advances have been made in understanding of gene structure and expression applicable to a spectrum of diabetes-related problems, from the development of the disease to the unlimited production of human insulin through recombinant DNA techniques. The first clinical trials of the effectiveness and safety of this synthetic human insulin have been initiated, and industrial production of such insulin for routine use in the management of diabetes is now contemplated.
- Substantial improvement has been made in our understanding of how insulin produces its effects on the body's tissues, including knowledge about the molecular events that occur from binding of the hormone to specific receptors on the surface of the cell to postreceptor intracellular actions.
- Significant technical advances have been made in the development and refinement of automated insulin delivery systems.
- Procedures for the successful transplantation of pancreatic islets from rats to mice without continuous immunosuppression and without short-term rejection of transplanted tissues have been developed.

Pathways of Research Progress

Etiologic factors in diabetes. Although the causes of insulin-dependent and noninsulin-dependent diabetes are not precisely known, significant progress has been made in identifying and elucidating several potentially important genetic and environmental factors related to the etiology of both types.

First, a variety of studies suggest the presence of a genetic component in both types of diabetes, but the inheritance patterns differ. Studies in identical twins, at least one of whom has diabetes, reveal that while the concordance rate approaches 100 percent in the noninsulin-dependent form, it is only about 50 percent in insulin-dependent diabetes. Recent epidemiologic studies indicate a strong association between insulin-dependent diabetes and certain genetically determined HLA tissue types, but such an association has not been found in noninsulin-dependent diabetes.

Studies have also demonstrated that viral infections in certain experimental animals with specific genetic backgrounds can cause extensive damage to pancreatic islets (where insulin is produced), resulting in insulin-dependent diabetes. Such studies provide a possible link between the genetic background of the individual and the susceptibility of the pancreatic islets to damage by viral infections. Recently, several common human viruses (mumps, Coxsackie B, and reoviruses) have been shown to be capable of inducing diabetes in laboratory animals, and human beta cells have now been grown in tissue culture and infected and damaged by these viruses. Scientists have also reported isolating a Coxsackie B virus from the pancreas of a young boy who succumbed to insulin-dependent diabetes, and subsequently producing diabetes by injecting the virus into genetically susceptible mice. Long-term systematic prospective studies in genetically susceptible children and siblings of patients with diabetes are now needed to explore the relationships between hereditary factors and viral infections that may relate to the cause of diabetes.

An immunologic component in the pathogenesis of insulin-dependent diabetes has been suggested by the observation that many patients with this type of diabetes have circulating antibodies directed against the insulin-producing islet cells in the pancreas. It is possible that viral infections may induce the production of islet cell autoantibodies in genetically predisposed individuals and that the subsequent damage to their islets is due directly to the virus. Alternatively, one form of insulin-dependent diabetes may be due to autoimmune factors. In contrast to the insulin-dependent form of the disease, islet cell antibodies are not found in noninsulin-dependent diabetes. These important observations provide the potential not only to elucidate the genesis of insulin-dependent diabetes, but also to develop rational approaches for the prevention of the disease.

Obesity is an important factor in noninsulin-dependent diabetes, since over 80 percent of patients with this type of diabetes are overweight when the condition is diagnosed. Obesity clearly aggravates diabetes, while weight loss is frequently associated with improvement in carbohydrate metabolism and normalization of symptoms. Although the mechanisms through which obesity is diabetogenic are not completely understood, the bulk of research evidence indicates that obesity tends to diminish the body's responsiveness to insulin, i.e., that it produces a state of insulin resistance. Additional research is necessary to define the relationship between diabetes and obesity and to develop therapeutic approaches to increase the effectiveness of insulin.

Insulin synthesis. The supply of insulin for diabetic patients has, until very recently, been derived solely from pork and beef pancreas. These sources of insulin

vary in composition, to a small degree, from human insulin. It is therefore thought that proteins present in pork and beef insulin preparations may be responsible for the formation of antibodies against insulin binding and the subsequent development of insulin allergy in some patients. In an effort to alleviate allergy to animal insulins, and as a means to assure adequate future supplies of insulin for the diabetic population, the synthesis of human insulin through the use of recombinant DNA techniques has become an area of active research interest and achievement.

One of the first practical spin-offs of recombinant DNA research has been the creation by Institute grantees of E. coli bacterial strains that will synthesize rat proinsulins (biologically inactive precursors of insulin) using a copy of the rat's natural gene for induction of insulin synthesis in the bacteria. This accomplishment was the forerunner of the subsequent production of a biological carbon copy of human insulin. Clinical trials of human insulin produced by this new and innovative technology have been initiated within the last year and will be carried out by Institute grantees. Although full-scale commercial production of human insulin from genetically engineered bacteria is still probably several years away, this new procedure holds potential for future mass production of human insulin, possible alleviation of insulin allergy, reduced cost of treatment, and assurance of adequate supplies of the human hormone for the diabetic population.

Insulin secretion. Abnormalities of insulin synthesis and/or secretion characterize both forms of diabetes: In insulin-dependent diabetes there is an absolute deficiency of the hormone, while in the noninsulin-dependent form, insulin secretion may be excessive, normal, or low. Glucose appears to be the primary physiological stimulus for insulin secretion, but it has not been established whether a metabolite of glucose or a metabolic cofactor, or possibly glucose itself, acts as the actual trigger for insulin secretion. Nevertheless, studies have demonstrated that glucose directly or indirectly stimulates a two-phase release of insulin, starting with a rapid initial peak followed by a slower secondary rise. It has been suggested that these two stages of insulin release may reflect distinct phenomena, each under separate, possibly converging regulatory control. In classic insulin-dependent diabetes, the islet cells do not respond to glucose stimulation in either phase; and in some forms of noninsulin-dependent diabetes, rapid-phase insulin release appears to be defective. With the ability to maintain islets in tissues cultured from insulin-dependent and noninsulin-dependent patients, studies to discover defects in the formation, storage, or release of insulin are now being carried out.

Action of insulin. Insulin is the major key to the control of normal levels of glucose in the blood. How insulin acts to maintain normal blood glucose levels has been the focus of many studies since the first active preparations were isolated in 1921. While the basic defect in insulin-dependent diabetes is an absolute deficiency of insulin secretion from the pancreas, in noninsulin-dependent diabetes it has been shown that the beta cells still produce some insulin and in many patients the defect appears to be ineffective action of the insulin in tissues, i.e., insulin resistance.

It is believed that insulin sets in motion a large number of cellular events in practically all body tissues, some related to the cell wall (such as glucose entry, amino acid and potassium transport, or a change in the electric charge of the membrane) and others involved with the synthesis and breakdown of proteins and other factors inside the cell. It was demonstrated that the initial action of insulin was to bind onto or interact with a site (receptor) on the cell membrane that has a very high specificity for the insulin molecule. This interaction apparently generates a signal or "second messenger" (the hormone itself is the first messenger) that activates various intracellular mechanisms responsible for insulin's biological effects. The second messenger (not yet identified for insulin) activates enzymes which are responsible for the synthesis or rapid breakdown of the storage form of glucose, glycogen (the latter for provision of energy), or the breakdown of stored fat for muscle energy use. Further research in this area is continuing in an effort to understand better the action of insulin, particularly for the benefit of the vast majority of noninsulin-dependent diabetics, in whom insulin is not absent, but in whom its action is impaired.

Insulin resistance. Insulin resistance can be defined as a condition in which higher concentrations of insulin are required to exert an effect on cells. This phenomenon is observed in some forms of noninsulin-dependent diabetes, particularly those associated with obesity, and also has been associated with glucocorticoid therapy, Cushing's syndrome, estrogen therapy, uremia, acromegaly, and pregnancy. Insulin resistance can be exhibited in a variety of cells in the body, such as muscle, liver, and fat cells. Institute grantees have shown that the mechanisms responsible for such defective insulin action may be related to decreased numbers of insulin receptors on the surface of cells or to defects at other sites within the cell on which insulin acts, i.e., postreceptor defects. Whatever the mechanism, higher levels of insulin are required to produce the biological events associated with insulin action. In some individuals, the excess insulin maintains normal glucose metabolism, while in others it does not and hyperglycemia ensues. It has been found that obese patients show a direct linear relationship between percentage of ideal body weight, the degree of insulin resistance, and the levels of circulating insulin.

Further investigations have provided insight into the importance of weight control in diabetics. Because of the findings of these studies, prevention of obesity and the aggressive treatment of overweight diabetics have become major principles in diabetes management. With weight loss, the efficiency of hormonal action has been shown to improve, leading to improved carbohydrate tolerance despite lower concentrations of insulin. These

findings have become the basis of the management of noninsulin-dependent diabetic patients.

Complications of diabetes. Diabetic patients at any age have mortality rates far higher than those for the general population because of the complications of diabetes. These complications are similar in both insulin-dependent and noninsulin-dependent diabetes, affecting primarily the large and small blood vessels, kidneys, eyes, and nerves.

It is not known definitely whether the complications are secondary to the high blood sugar levels and abnormal metabolism that characterize diabetes or whether diabetes and the complications are manifestations of a more basic underlying disease process. Recent studies in laboratory animals support the idea that the abnormal metabolic conditions of diabetes influence the development of the complications. These studies suggest that fine control of blood sugar may prevent or delay diabetic complications. This evidence is less clear in man, and, although preliminary data hint at a similar relationship, much more research is required.

The conventional method of administering insulin by daily injection in the treatment of diabetes does not duplicate the complex system by which human hormone secretion is finely adjusted to the demand created by varying diet and exercise levels in the nondiabetic. In normal individuals, the blood sugar level remains within a remarkably narrow range throughout the day, a range that for all practical purposes is impossible to attain in the diabetic by the usual methods of treatment with insulin. One of the major unresolved issues in clinical diabetes is whether the elevated blood glucose levels typically seen in the diabetic are causally related to the long-term complications of this disease, and whether these complications could be delayed or prevented if the blood sugar level were normalized. This issue has stimulated the design of instrumentation for delivering insulin in a more physiological fashion, permitting near normalization of the blood sugar level in diabetics for prolonged periods.

Pancreatic islet cell transplantation. The ability to replace pancreatic islets that either have been totally destroyed or are otherwise functionally defective would be a tremendous advance in the treatment of diabetes. This procedure has not been carried out successfully in man, primarily because of the phenomenon of immunological rejection of transplanted tissue. Remarkable accomplishments in the field of pancreatic islet transplantation in animals have occurred in recent years.

Pancreatic islets have been transplanted successfully into highly inbred strains of diabetic rats, with complete cure of their diabetes as a result. Further, within the last year, NIADDK-supported investigators have developed a procedure for successful transplantation of islets from one animal species (rat) to another (mouse) with greatly delayed and only very gradual immune rejection of the transplanted tissue. In these studies, healthy rat islets were isolated and placed in tissue cultures to lessen the rejection-inducing capability of immunologically active cells present in the islet tissue.

These animal studies represent a significant advance in the fields of immunology and organ transplantation and offer hope that, in the continuing search for better methods of treating diabetics who depend on insulin injections for survival, the problems of immunological rejection can be overcome and human application of the procedures established. It will still remain to be demonstrated, however, that such improved treatment will prevent or ameliorate the complications of diabetes.

Insulin delivery systems. Two general classes of insulin delivery instruments have been developed. One of these, referred to as a "closed-loop" system, consists of a glucose sensor, an insulin pump, and a computerized control circuit that regulates the rate of insulin administration as a function of measured glucose. At the present stage of development, closed-loop systems are large, complex devices which virtually immobilize a patient in a bed or chair and can therefore be used only on an inpatient basis for treatment of acute emergencies or for short-term experimental studies. Further development of refined, miniature closed-loop systems is limited by a number of factors including the lack of a reliable and specific glucose sensor with physical and biological characteristics that would permit prolonged function once implanted in the body.

The other type of device, the "open-loop" system, essentially consists of an insulin pump and a control circuit that regulates the rate of insulin infusion according to a preprogrammed pattern. Delivery of preset, greater quantities of insulin prior to meals can be programmed for automatic delivery, or delivery can be induced by the patient's pushing a button at the desired times. Institute grantees have developed a number of prototype open-loop devices which are portable and now offer the potential for use in long-term ambulatory studies.

During the past year, development of a totally implantable, refillable insulin delivery device has been reported. Regulation of the insulin delivery rate can be accomplished either manually through a magnetically activated valve or by telemetry from a remote, programmable electronic controller.

The successful development of open-loop devices now permits long-term studies evaluating the relationship between strict normalization of blood sugar levels for prolonged periods of time and the development of diabetic complications. A major clinical trial will be initiated by NIADDK in the near future.

Animal models. Animal models are extremely important as tools for diabetes research. While a given model may not duplicate every aspect of the human disease, once an answer to a question has been obtained in an animal model, it generally will be possible to devise one or several indirect means of testing for the applicability or nonapplicability of that answer in human diabetics or a specific type of diabetic patient. Consequently, NIADDK supports the development of inbred strains of animals (such as several breeds of mice, rats, and hamsters) carrying various single gene mutations causing diabetes or diabetes-like syndromes.

Appropriate matings can be made that will produce predictable numbers of unaffected and diabetic animals, all of which are of the same strain, differing only by a single gene—a feature that greatly facilitates interpretation of biochemical and morphological results. Having several single genes that can cause identical diabetic conditions in animals could greatly aid the unraveling of the nature and types of metabolic defects that can lead to diabetic states in humans. Also, an understanding of the mode of action of the modifying genes in the various inbred strains that change the course of the disease from a severe insulin-dependent type to a mild noninsulin-dependent type would be an important contribution to the understanding of human diabetes variants.

Program Accomplishments

Diabetes centers program. An important facet of the NIADDK diabetes program has been the establishment of centers, begun in 1973 with Diabetes-Endocrinology Research Centers and expanded in 1977 to include the legislatively mandated Diabetes Research and Training Centers. NIADDK is currently supporting three DERCs and eight DRTCs.

The centers are supported at institutions where there is an established strong base of high-quality ongoing biomedical research in diabetes and related endocrine disorders. The center funding primarily provides core facilities or shared resources for the individual investigators in order to strengthen existing programs, increase productivity, and foster the generation of new ideas and innovative research approaches.

Another feature of the centers program is the funding of pilot and feasibility studies which allow researchers to explore the feasibility of a new concept for up to 3 years. While primarily for young investigators, this mechanism may also be used by established investigators in other fields to test the applicability of their expertise to the field of diabetes.

While in both the DERCs and the DRTCs, the major emphasis is on biomedical research, the DRTCs have an added component responsible for translating research results into applications that will have their ultimate impact in improved care and management of the diabetic patient or in the prevention and/or cure of diabetes. The DRTCs achieve this goal through their training and information transfer component, which provides for the development and dissemination of improved education methods for physicians and allied health professionals responsible for the treatment and management of patients with diabetes.

The DRTCs have established an environment that fosters and integrates the efforts of basic and clinical scientists, physicians, allied health personnel, and educators joined together in a cooperative, multidisciplinary approach to the many research and health care problems associated with diabetes and its complications. In this regard, the DRTCs provide a national resource, and relationships have been established between the centers and other Federal agencies that support diabetes-related programs, e.g., with nearby State Diabetes Control Projects (organized and funded by the Centers for Disease Control), and with the Health Services Administration's Indian Health Service (IHS) Diabetes Model Care Projects.

National Diabetes Data Group. The National Diabetes Data Group serves to foster, coordinate, and integrate national resources for the collection and analysis of data on diabetes to provide a sound basis for the development of scientific research priorities and the planning of public health programs. The data group also continues to provide the Federal focus to which both the lay and scientific communities turn for accurate, reliable statistics on diabetes.

The National Diabetes Data Group consists of a nationwide group of expert advisors that includes epidemiologists; individuals with expertise in the research, nutritional, and socioeconomic aspects of diabetes; and representatives from Federal agencies (the National Institutes of Health, the Centers for Disease Control, the National Center for Health Statistics), the National Diabetes Advisory Board, and the private sector (the American Diabetes Association and the Juvenile Diabetes Foundation).

The data group recently convened an international work group that formulated a consensus on a uniform classification of diabetes, appropriate diagnostic criteria, and standard terminology to be used as a guide for clinical and epidemiologic research. This classification has now been adopted by the American Diabetes Association and the World Health Organization's Expert Committee on Diabetes.

The data group has recently assessed the changing mortality rates for diabetes, particularly the rapid decline in the cardiovascular disease death rate among diabetics, and its analysis uncovered a shift away from the cardiovascular diseases and toward noncardiovascular conditions as causes of death of diabetics. In addition, the data group developed a compilation of statistics on morbidity and mortality attributable to the complications of diabetes and on aspects of medical care and health services for diabetics, which served as the quantitative basis for the recent recommendations of the National Diabetes Advisory Board on programs to reduce morbidity and mortality from diabetes and its complications. The data group works in close collaboration with the National Center for Health Statistics in assessing the national diabetes data collected by that agency and in planning future surveys.

National Diabetes Information Clearinghouse. The National Diabetes Information Clearinghouse was established by NIADDK in September 1978. It serves as the central resource for the collection and dissemination of information about educational and scientific materials, programs, and other resources relevant to diabetes. The clearinghouse serves and interacts with the Diabetes Research and Training Centers; local, regional, and national diabetes organizations; professional groups; state departments of health; and other Federal agencies.

The NDIC has three major goals: to increase the availability of accurate diabetes information for health care professionals, patients, and their families; to increase community awareness and understanding of diabetes as a major health problem; and to establish a viable system for speeding communication about new developments, techniques, and programs in diabetes among all sections of the diabetes community.

Since its inception, the NDIC has abstracted and indexed over 2,500 diabetes educational brochures, booklets, and other materials. These materials have been categorized into subject areas and compiled into 14 topical annotated bibliographies ranging from 30 to 130 items. Included are topics such as care of the foot in diabetes, educational materials for and about young people with diabetes, cookbooks for diabetics, pregnancy, materials for and about the visually impaired, and Spanish-language materials. The NDIC has also compiled a directory of state and Federal resources for people with diabetes and has produced the proceedings of a conference on behavioral and psychosocial issues in diabetes.

The clearinghouse cooperates closely with Federal and state agencies, voluntary organizations, and health professionals to develop strategies to increase community awareness and understanding of diabetes as a major health problem and to encourage effective patient, family, and community education programs.

ENDOCRINOLOGY

Endocrinology is the science that concerns itself with hormones—chemical agents that are secreted into the blood from ductless glands which act at distant target sites in the body to control important body functions. Because this area of investigation is intimately related to the more basic areas of biochemistry and cellular and molecular biology, progress in the clinical aspects of endocrinology, perhaps more than in any other field of medicine, is closely tied to advances in the basic biomedical sciences.

Hormones induce a vast array of biochemical effects in their target tissues that, in aggregate, influence all body tissues and organ systems. They regulate the growth of skeletal and soft tissue; strongly affect the maturation and function of the central nervous system; determine the physical and behavioral aspects of gender; and critically influence virtually every phase of the reproductive process. Hormones set the level of the basal energy requirement and are a major influence on the metabolism of sugars, fats, and proteins. They play a critical role in responses to environmental alterations (such as changes in temperature or the availability of food), to physical or chemical injury, and to infectious agents and immunological challenges. Acting in concert with the nervous system, with which it is closely associated, the endocrine system integrates these responses in a manner most beneficial to the individual.

The field of endocrinology encompasses disorders that are among the most common in all of medicine—diabetes, thyroid diseases, and growth and reproductive disorders—diseases that have an enormous impact on human health and well-being and on the costs of medical care. Endocrine factors also play an important role in the causation, manifestation, and treatment of diseases that are primarily attributed to other organ systems and that are major causes of death and disability—

Highlights of Recent Advances

The following summarizes advances from recent years in endocrinology research.

- Research on the actions of human growth hormone and organization of its supply from natural sources now permits the successful treatment of children with hypoactive pituitary glands so that they reach the lower levels of normal height rather than being condemned to lifelong dwarfism.
- Research on adrenocorticotropic hormone shows that while the hormone is produced as a large molecule in the pituitary, it can be broken down into several smaller biologically active peptides found in different tissues throughout the body.
- Basic research involving recombinant DNA techniques has made it possible to produce human growth hormone with the aid of genetically engineered bacteria. Future commercial production of the hormone by this method will make it possible to treat all children afflicted with hypopituitary dwarfism to achieve near-normal or normal height.
- The endorphins, a group of naturally occurring opiate-like substances in the brain, have been identified. They are thought to have a role in a number of areas, including mood regulation and pain relief.
- Studies of cell surface membrane receptors and new findings on activated hormone-receptor complexes are opening the door to understanding hormonal mechanisms of action.
- Vitamin D is now known to be metabolized successively by the liver and kidney to form the metabolite 1,25 dihydroxyvitamin D, which plays a significant endocrine role in the regulation of calcium metabolism. The role of this newly discovered hormonal system in various diseases involving mineral metabolism is being elucidated.
- Studies on prostaglandins have demonstrated their ubiquitous distribution in the body as well as their hormone-like activity.

diseases such as atherosclerosis, cardiovascular disorders, cancer, and psychiatric disorders. Not surprisingly, some form of endocrine research is supported by each of the Institutes at NIH.

NIADDK's endocrinology program supports basic and clinical research on the normal and abnormal functioning of the endocrine glands; the structure, function, and mechanism of action of the hormones produced; the effects of the hormones on various processes in the body; and the factors that relate to or modify the effects of the endocrine system.

The achievements of research in endocrinology and endocrine disorders during the last three decades have been impressive: thyroid abnormalities can be diagnosed and treated promptly and effectively, and hormonal deficiencies such as Addison's disease and certain types of dwarfism can be recognized and corrected through specific replacement therapy. Within recent years, these and other significant advances have helped to elucidate the mechanisms that serve as the bridge and controlling pathway between the nervous and endocrine systems.

Pathways of Research Progress

Human growth hormone synthesis. Human growth hormone, secreted by the pituitary gland, is necessary for normal growth and development and is used for treatment of growth disorders such as hypopituitary dwarfism. To date, the only large source of this hormone for therapy is human pituitary glands, which are collected at autopsy and from which the hormone is extracted. However, clinical trials are to start soon with human growth hormone produced by recombinant DNA techniques using bacteria. These trials will test the effect, potency, and any side effects of the bacterially produced hormone. Initial studies indicate that the hormone extracted from human glands and the material produced in bacteria are very similar, if not identical. If the clinical trials confirm the initial results, it is expected that more human growth hormone will be available for both therapeutic purposes and research. There are indications that growth hormone has effects in addition to its growth-stimulating effects, but research into these other effects has been held back by the need for the hormone in clinical research on short stature. With increased supplies of the hormone, it is expected that research opportunities will expand in the future.

Growth factors. It has long been known that growth hormone exerts some of its effects via the somatomedins. Somatomedins are defined as substances under growth hormone control that have both growth-promoting and insulin-like effects. They consist of several low molecular weight peptides known as somatomedin A, somatomedin C, insulin-like growth factor (IGF), and multiplication stimulating activity (MSA). The Institute supports several studies on these and other growth factors in an effort to learn more about their mechanism of action. Recent research has shown that these growth factors circulate bound to carrier proteins of fairly high molecular weight, but the role of the carrier protein is unclear. In studies with children, it has been shown that IGF levels are the same as in adults after about 4 years of age; however, the carrier protein level is significantly lower in children than in adults. This might be interpreted to mean that the unbound growth factors in children are available for growth. In adults, with more carrier protein, the growth factors are bound, and thus not as readily available for growth promotion. Much research remains to be done in the general area of growth and growth factors to answer this and many other questions on control of growth.

Calcium and calmodulin. Calcium has long been known to be an important factor in normal body function. Its most obvious role is as part of the mineral structural component of the skeleton. There are many other, more subtle calcium-dependent processes in the body, but exact mechanisms are largely unknown.

Calmodulin is a recently described, ubiquitous binding protein for calcium that seems to play an important intermediary role in many calcium-dependent processes. Calmodulin first binds free calcium, and then binds to a number of enzymes, inducing conformational changes and thus endowing these enzymes with calcium sensitivity. Among the enzymes affected by calcium-calmodulin are phosphodiesterase and adenylate cyclase. These enzymes appear to regulate the intracellular levels of both cyclic AMP and cyclic GMP, substances that can act as "second messengers" to hormone action. Through their effects on phosphodiesterase and adenylate cyclase, calcium and calmodulin clearly figure prominently in normal body function, but more research is needed to further elucidate the precise mechanism of their actions.

Biological fate of ACTH. Adrenocorticotropic hormone is a large molecule produced in the pituitary which primarily stimulates the adrenal glands to synthesize steroids, but which has been found to have a variety of other effects. In the past 10 years, it has become apparent that ACTH can be broken down into several biologically active peptides. The "master molecule" contains ACTH and beta lipotropin in the form of one long chain of amino acids. The ACTH portion of the "master molecule" may be further cleaved to form alpha melanocyte stimulating hormone and corticotropin-like intermediate lobe peptide. The beta lipotropin portion of the "master molecule" can be cleaved to become gamma lipotropin and beta endorphin, and these molecules can be broken down even further to alpha endorphin and beta melanocyte stimulating hormone. Melanocyte stimulating hormones are important in the distribution of pigment and darkening of the skin, and the endorphins are a recently discovered group of naturally occurring, opiate-like substances which may play a role in a variety of functions including relief of pain.

These studies are important because the various peptides derived from the precursor ACTH molecule are found in many different tissues throughout the body. Further, this may indicate that different tissues respond

to the same precursor in different ways, utilizing only those portions of the larger molecule that they need for their specific function.

Membrane receptors. Glycoproteins (complex carbohydrate structures attached to protein backbones) make up a large proportion of the components of cell membranes and are necessary for normal cell function. These cell membrane glycoproteins appear to provide an array of "antennae," or receptors, on the cell surface that function primarily to interact with hormones, metabolites, and other effectors and to initiate the transmission of signals to the cell to regulate cell growth, metabolism, and differentiation, as well as immunological responses. Recent work has now established that the carbohydrate portions of these glycoproteins are essential for the normal positioning of proteins in the membrane, for the mobilization and "packaging" of the proteins that are secreted, and for the specificity of the interaction with constituents outside the cell.

In addition, recent research has shown that the outer, plasma membrane of the cell is fluid and that receptors are free to move over the cell in the plane of the membrane. This molecular motion of the membrane receptors can be modulated; that is, the receptors can be either redistributed by cross-linking or anchored reversibly after interacting with membranous structures. It appears that this modulation is mediated by cytoplasmic microfilaments and microtubules associated with the plasma membrane in a dynamic fashion. Studies of receptor composition and mobility are important to our understanding of the modulation of a variety of cellular phenomena in many types of tissues.

Prostaglandins as "second messengers." Cyclic adenosine monophosphate (cAMP) functions as a "second messenger" within the cells of target organs, translating the first message obtained from peptide hormones from outside the cell into action in cellular organelles or the nucleus. In addition to cAMP, there is a second complex class of intracellular messengers, the prostaglandins. Prostaglandins are oxygenated derivatives of unsaturated fatty acids. They appear to be produced in nearly every organ and seem to have effects both locally and at distant organ sites. Prostaglandins have been shown to have many actions including mediation of the inflammatory response, stimulation or inhibition of intravascular blood clotting, and influence over ovarian function and the menstrual cycle. Prostaglandins also seem to enhance the resorption of bone, affect gastric acidity, and influence bronchial smooth muscle tone. Because of their widespread distribution in the body and their hormone-like actions, locally and at target organs, research in prostaglandins and their actions will continue in the future with NIADDK support from the endocrinology program.

Vitamin D and calcium metabolism. Major advances in our understanding of the regulation of mineral metabolism have recently been made through NIADDK-supported studies on the newly discovered metabolite of vitamin D—1,25 dihydroxyvitamin D. This sterol hormone is produced from vitamin D in response to situations of calcium and phosphorus need, with the final enzymatic reaction occurring in the kidney. In concert with the other known calcitropic hormones (parathyroid hormone and calcitonin), the 1,25 hormone mediates calcium and phosphorus metabolism at target tissues including intestine, bone, and kidney.

The now recognized role of the kidney in vitamin D metabolism in concert with other recent research has helped clarify the pathophysiology of a number of unsolved metabolic bone diseases, including renal osteodystrophy. Synthetic analogues of active vitamin D metabolites have been used therapeutically to treat several known mineral diseases associated with vitamin D metabolism.

Program Accomplishments—National Hormone Distribution Program

In 1958, a milestone in the treatment of pituitary dwarfism was achieved with the successful growth stimulation of a child who had a deficiency of growth hormone. The needed growth hormone was extracted from human pituitary glands collected at autopsy. This achievement signaled a new era in clinical endocrinology.

At present, human pituitary glands removed at autopsy still provide the only source of human growth hormone, and because the equivalent of at least 30 to 50 pituitary glands per year are required to treat each child, this important hormone is still in generally limited supply.

To increase the availability of human growth hormone for clinical research, the National Pituitary Agency was established by NIADDK in 1963. Since then it has evolved into the National Hormone Distribution Program and is still supported by the Institute. Through the cooperation of the College of American Pathologists, the NHDP collects pituitary glands from hospitals and medical centers around the country, extracts a number of hormones from them, and distributes them for use in clinical and basic research programs throughout the United States.

Despite this expansion, human growth hormone is still in short supply, and all patients receiving it through the NHDP must do so in research centers. Recent developments in recombinant DNA technology, largely supported by NIADDK, promise to change this situation through the production of growth hormone by bacteria.

In addition to growth hormone, the NHDP supplies the following scarce human hormones to investigators: follicle stimulating hormone, luteinizing hormone, thyroid stimulating hormone, prolactin, adrenocorticotropic hormone, and lipotropin. The program also makes available corresponding pituitary hormones from the rat and sheep for endocrine research in these valuable animal models. This nationwide effort for the coordination and distribution of scarce research resources is of inestimable value to patients with hormone deficiency states and to endocrinological research in general.

METABOLIC DISEASES

Metabolism is often defined as the total of all the biochemical and enzymatic reactions occurring in the cell. More accurately, metabolism is an extremely complex, highly coordinated, purposeful activity in which many sets of interrelated multienzyme systems participate, exchanging both matter and energy between the cell and its environment. Metabolism has four specific functions: to obtain chemical energy from fuel molecules; to convert nutrients into building blocks, or precursors, of cell components; to assemble such building blocks into proteins, nucleic acids such as DNA and RNA, fats, and other cell components; and to form and degrade molecules required in specialized cell function.

Fiscal, humanitarian, and scientific considerations are compelling stimuli to the support of research on inborn errors of metabolism, in which there is a defect in the synthesis of a given enzyme required for normal metabolic regulation. Biomedical science has long recognized and taken advantage of the fact that genetically determined disorders of metabolism afford unique and invaluable opportunities for the elucidation of both normal physiological pathways and the pathogenesis of disorders within them. Although individually uncommon, genetically determined disorders have profound public health impact. Approximately 30 to 40 percent of all admissions to children's hospitals are attributable to such disorders, and they account for approximately one-third of all infant deaths in the United States. In addition, more than one-third of patients in state hospitals for the mentally retarded have genetically determined disorders, incurring costs for care in excess of $1 billion annually. Patients hospitalized for just one such disease, phenylketonuria, would incur a net cost over current treatment of $50 million annually, were it not for programs of neonatal detection and dietary therapy.

Scientific progress in this general area has had a favorable impact on health, well-being, and the costs of medical care. Advances in the recognition and understanding of inherited metabolic diseases, together with the development of increasingly sensitive and sophisticated biochemical techniques for their detection, have greatly facilitated prevention, early diagnosis, and treatment to circumvent or reverse the effects of enzyme deficiency.

As basic and clinical research in metabolism and cellular function underlies most biomedical research investigations, NIADDK's metabolic diseases program supports a broad range of investigations pertaining to understanding the etiology, pathogenesis, prevention, diagnosis, and treatment of metabolic diseases. The research areas relevant to the program's goals include normal and pathological metabolic pathways, enzyme structure and function, cellular oxidations and biological membranes, synthesis and biosynthesis of relevant biological substances, and the utilization of modern instrumentation in metabolic disease research.

Highlights of Recent Advances

The following highlights present some of the more recent advances in the rapidly evolving field of metabolic diseases research.

- Improvements in early diagnosis and clinical management of patients with cystic fibrosis have dramatically increased the life expectancy of patients with this ultimately fatal, inherited metabolic disease.
- New tests are being developed which may enable investigators to detect carriers of cystic fibrosis and to detect the presence of the disease prenatally.
- Findings on the role of enzymes in severe combined immunodeficiency disease have led to a new approach to cell growth inhibition.
- Investigators have identified a new error of metabolism resulting in accumulation of methionine.
- Scientists have identified two new animal models useful for study of some human lysosomal storage diseases.

Pathways of Research Progress

Cystic fibrosis. Cystic fibrosis, the most common lethal genetic disease of Caucasian populations, appears to be an inborn error of metabolism involving all exocrine glands and, most likely, other tissues and organs. The characteristic generalized dysfunction of the exocrine glands results in a clinical picture of recurrent pulmonary disease, pancreatic insufficiency with malabsorption of nutrients, and elevated sweat electrolyte concentrations. Numerous other organs are also affected in a primary or secondary fashion. The key to improved survival appears to be early diagnosis and aggressive antibiotic therapy; approximately 90 percent of deaths from CF are still attributable to pulmonary disease.

It is estimated that the heterozygote (carrier) rate in the population is 1 in 20 persons. Unfortunately, however, the basic genetic defect responsible for this disease is still not known, and a commonly applicable, reliable test for the detection of carriers or for prenatal diagnosis does not exist. For these reasons, cystic fibrosis research is an area of long-standing, increasingly intensive investigation and support by NIADDK. Investigations conducted and supported by NIADDK and other NIH Institutes are aimed specifically at defining the cause and physiological effects of cystic fibrosis and the associated biochemical aberrations, and at improvement of methods for prompt diagnosis, more effective treatment, recognition of carriers for the disease, and eventual prevention of the disorder.

In 1954, Institute scientists and others discovered the sweat gland abnormalities associated with CF and developed the only reliable diagnostic test for it, the

sweat test, which shows markedly elevated values for both sodium and chloride in patients with CF. Current studies at several laboratories on heterozygote detection and prenatal diagnosis have prompted guarded optimism; however, none of the new detection methods developed to date has as yet seen widespread clinical application.

The greatest strides in decreasing morbidity and mortality have been made clinically. Current therapy is only symptomatic and prophylactic; however, with aggressive multisystem treatment—use of antibiotics, bronchodilators, mucolytic agents, postural drainage, pancreatic enzyme supplementation, and nutritional counseling—many patients are surviving into adulthood, whereas as little as two decades ago the disease was almost uniformly fatal in early childhood.

Phenylketonuria. Phenylketonuria (PKU) is an inherited metabolic disease resulting from the disordered metabolism of the amino acid phenylalanine, essential for protein synthesis in human tissues. Infants who lack a liver enzyme (phenylalanine hydroxylase) for metabolism of this amino acid accumulate this substance in their tissues, with the almost inevitable result of severe, irreversible brain damage. NIADDK scientists were the first to recognize the etiology of PKU as a deficiency in phenylalanine hydroxylase, and subsequently a special diet was developed that, if started early enough in life, could prevent or arrest development of the ensuing mental retardation.

The latest important advance in the control of PKU is the development of a simple and reliable finger-prick blood test that now makes it possible to diagnose PKU babies within the first few days of life. Mass screening of newborns has been so successful that almost every state in the country now has laws mandating the testing of all babies within the first 72 hours of life and the immediate institution of dietary therapy for affected individuals.

Wilson's disease. Wilson's disease (hepatolenticular degeneration) is a rare autosomal, recessively inherited disease that is usually fatal unless recognized early and treated aggressively. This insidious disorder is caused by the body's inability to limit the absorption of copper from the diet or to eliminate copper already absorbed. The untreated disease is invariably associated with excess deposition of copper in the tissues, particularly the liver, brain, cornea, and kidney, where copper accumulation causes progressive and irreversible degeneration.

NIADDK scientists have made considerable progress in detecting and treating this disease. Treatment consists of a low copper diet to which potassium sulfide is added to prevent absorption of copper. Oral penicillamine is also given to promote urinary excretion of copper already deposited.

In addition to developing a specific diagnostic test for the active clinical disorder, investigators have also discovered a method for determining the presence of Wilson's disease in the early, asymptomatic stage. Further, they have devised a technique to identify carriers of the disease. The latter technique, which is of value in genetic counseling, depends on the degree of incorporation of radioactively labeled copper into the blood plasma protein ceruloplasmin. The early identification of carriers of this disease can alert physicians to the appearance of Wilson's disease in children at a time when treatment can be instituted and full expression of the disease's wide-ranging symptoms prevented.

Galactosemia. Galactosemia is an inherited metabolic disease characterized by abnormally high levels of the milk sugar galactose in the blood of the patient and an inability to metabolize galactose. The disorder becomes manifest during the first few weeks after birth by the infant's intolerance to milk. If milk is fed to a galactosemic child for any length of time, the illness leads progressively to cirrhosis of the liver, mental retardation, blindness due to cataracts, and death. Individuals with this disorder account for more than 1 percent of those cared for in the Nation's mental institutions.

In 1959, NIADDK scientists discovered the mechanisms underlying galactosemia. Further work by Institute scientists led to the development of a diagnostic test whereby detection of galactose in the urine or blood makes the screening of large populations possible. These investigations have also led to the development of special diets that permit normal physical and mental development of the afflicted child.

Mucopolysaccharidoses. The mucopolysaccharidoses are but a few of the disorders known collectively as inherited diseases of connective tissue. The common feature of this entire disease group is that some element of connective tissue (collagen, elastin, mucopolysaccharide) is altered due to an apparent inborn error of metabolism and growth. Cultured skin fibroblasts are being used by researchers as a means of identifying additional variants of the human mucopolysaccharidoses—which include Hurler's, Hunter's, and San Filippo syndromes and other forms of mucopolysaccharide disease. These scientists are searching for specific enzymatic defects in patients, using known chemical structures of compounds deposited and excreted in these diseases. Identification of an underlying enzymatic deficiency could lead to isolation, purification, and synthesis of the crucial enzyme, which may then be administered to patients to counteract their metabolic deficiencies (enzyme replacement therapy). In addition, assays of cultured skin fibroblasts may provide a means of early detection, which in turn would be a basis for prevention of some of these inherited catastrophic diseases.

DIGESTIVE DISEASES AND NUTRITION

ESOPHAGEAL, GASTRIC, INTESTINAL, AND PANCREATIC DISEASES

Investigations in the esophageal, gastric, intestinal, and pancreatic diseases program areas are directed at the structure, function, and diseases of the salivary glands, esophagus, stomach, small and large intestines,

and pancreas. Disorders of particular concern are ulcer disease, ulcerative colitis and Crohn's disease, intestinal malabsorption syndrome, sprue, diarrhea, acute and chronic pancreatitis, and Zollinger-Ellison syndrome. Also included are general studies of the gastrointestinal hormones. Research goals include a better understanding of the basic physiological and biochemical processes associated with the normal and diseased conditions, as well as an increased ability to prevent, diagnose, and treat such disorders.

One of the most common and serious of these disorders, if left untreated, is peptic ulcer, a noncancerous, crater-like erosion in the wall of the stomach or intestine. Peptic ulcers occur only in those regions of the gastrointestinal (GI) tract that are bathed by the stomach's digestive juices, which contain hydrochloric acid and the protein-digesting enzyme pepsin—hence the name "peptic ulcer." Treatment for ulcer is generally designed to decrease the amount of peptic secretions that reach the ulcer and interfere with the normal healing process.

Intensive research by NIADDK-supported scientists has also been directed toward uncovering the causes of ulcerative colitis, which remains one of the outstanding unsolved problems involving the large intestine. Of particular interest has been the role of the immune system in the etiology of this disease and its complications. Although conclusive results have not yet been obtained, progress has been made in methods of therapy for ulcerative colitis. For example, Institute-supported investigators have completed a 10-year trial of treating patients with local, rather than systemic, corticosteroid drugs in the form of suppositories and enemas. They have shown that such procedures are superior to other methods of steroid drug administration in improving the course of the disease in cases involving primarily the lower colon. Other NIADDK grantees have reported that a nitrogen-mustard-like drug used primarily against cancer can also produce dramatic improvement in patients with chronic ulcerative colitis and regional enteritis.

Diarrheal disease is the world's leading killer of infants and children and is particularly lethal in areas of malnutrition, where resistance is low. It has received increasing research attention over the past two decades. Study of the toxin produced by the bacteria that cause cholera, a diarrheal disease not often found in the United States, has led to further understanding of fluid absorption and secretion by the intestine. Recently, evidence has been found that in the "secretory" diarrheal diseases, such as cholera and **Escherichia** coli toxin-mediated diarrhea, the intestine is stimulated by a toxin to actively secrete fluid. The toxin appears to bind to receptors on cell surfaces and stimulate certain enzymes that trigger the secretion of excess fluid. This information on the fundamental mechanism involved may permit the development of drugs to inhibit or block excessive intestinal secretions. Preparation of vaccines similar to those available for cholera now appears feasible for **E. coli**-mediated diarrhea.

Highlights of Recent Advances

Some of the most recent advances made by NIADDK scientists and grantees in the study of esophageal, gastric, intestinal, and pancreatic diseases are summarized below.

- The compound tiotidine has been shown to be several times more powerful in its action than previously used drugs and shows great promise in the inhibition of food-stimulated acid secretion in duodenal ulcer disease.
- New developments in the control of upper gastrointestinal hemorrhage involve the endoscopic spraying of blood-clotting factors to form a clot instantly at the site of bleeding. The procedure is now ready for testing in patients for whom surgery is deemed inappropriate.
- Recent research supported by NIADDK has determined that certain members of a class of compounds called prostaglandins play a role in protecting the stomach against gastric ulcers. Institute grantees have made significant advances in our understanding of the physiological action of specific prostaglandins on the lining of the stomach.
- Growth retardation, a characteristic of young patients with Crohn's disease, has successfully been reversed in a group of children with this disorder
- Evidence suggests that a viral agent or agents could play a causative role in inflammatory bowel disease.
- The interrelationships of various hormones in regulating growth in the gut and related organs have been described.
- Investigators have demonstrated that prostaglandins decrease the mortality rate and some of the biochemical changes that accompany acute experimental pancreatitis.
- In patients with Zollinger-Ellison syndrome, cutting the nerve supply to the gastric glands and administering the drug cimetidine appears to be a safe, effective alternative to conventional total gastrectomy
- A simple, sensitive diagnostic test for malabsorption disease has been developed that obviates the need for numerous biopsies.
- The drug cimetidine has been shown to be a valuable new therapy for patients with short bowel syndrome

Research on the pancreas has lagged behind that of other digestive organs, perhaps explained in part by the

erroneous notion that exocrine pancreatic diseases are uncommon, by the relative inaccessibility of the pancreas for clinical investigation, and by the lack of specific and rapid methods to study pancreatic function. As a result, we currently have no ability to diagnose early stages of pancreatic disease and treatment methods have scarcely changed over the past 30 years.

In acute pancreatitis (inflammation of the lining and tissues of the body of the pancreas), digestive enzymes inadvertently escape into the pancreatic tissue, which they proceed to digest and destroy. Causative factors postulated to trigger these self-attacks include alcoholism, gallstones, biliary tract disease, drugs, cigarette smoking, and disturbances of fat metabolism. Further knowledge of the mechanism by which activation of enzymes occurs in pancreatitis could lead to the development of specific inhibitors of these enzymes. The hormonal control of pancreatic secretion is being more actively explored as pure hormones are now available and because the secretions can be collected by direct insertion of a tube into the pancreatic duct. This is accomplished via endoscopy, and thus without surgery. In addition, some animal models of acute pancreatitis have been developed that may prove helpful in testing new strategies to deal with this severe disease.

Pathways of Research Progress

New insights into gastrin. Some of the most stimulating research in the area of digestive diseases relates to the study of gastrin, the hormone that stimulates secretion of gastric "juice" containing hydrochloric acid and gastric digestive enzymes. The isolation, characterization, and subsequent synthesis of gastrin accomplished by Institute grantees have provided an important tool for studying peptic ulcer, which may involve an excess of acid secreted by the stomach. Also, recent advances in radioimmunoassay methods have now made it possible to measure the hormones involved in the control of gastric secretion, paving the way to identifying the physiologic abnormalities in different types of ulcer disease and to devising appropriate therapies.

In recent years, Institute grantees have demonstrated the effectiveness of certain antihistamines and prostaglandins in blocking or inhibiting gastric acid secretion in patients with peptic ulcer. Between 1970 and 1978, hospital admissions for duodenal ulcer decreased by 43 percent, and deaths from peptic ulcer decreased by 31 percent. Improvements have also been made in conventional antacid therapy.

Another avenue of approach to the ulcer problem has been study of the factors governing the secretion of the protective mucus that bathes the inner linings of the stomach and intestine, and the repair and regeneration of the mucosa. One recent study, for example, suggested that there may be differences in the rate of replenishment of intestinal cells in patients with various digestive diseases. Other research has sought to determine the qualitative or quantitative differences in the protective qualities of gastric mucus of ulcer patients.

Prostaglandin protection in ulcers. Prostaglandins are widely distributed compounds synthesized in the body from certain polyunsaturated fatty acids. Although their biological significance is not yet entirely clear, they are being utilized in current studies for their special role in protecting the mucous lining of the stomach and intestine from injurious agents either ingested or found within the body. Drugs that inhibit the synthesis of prostaglandins, including aspirin and the numerous aspirin-like drugs in clinical use, tend to produce injury to the gastric mucosa, a major problem in the use of such drugs. Chronic ingestion of aspirin, for example, can cause not only acute erosions of the mucosa but also chronic gastric ulcer. Preliminary clinical trials have shown that prostaglandins are effective in treatment of these lesions and ulcers, but the exact mechanism of action is not known. Although prostaglandins inhibit acid secretion, they are effective in doses that do not inhibit acid, and some prostaglandins that do not inhibit acid are protective also. Researchers have suggested that the protection may involve stimulation of blood flow or stimulation of mucus and bicarbonate secretion by surface epithelial cells in the gut wall, both of which are protective against the corrosive action of gastric acid on the stomach lining. Research on these possibilities continues.

Growth and regeneration of gastrointestinal mucosal cells. Little is known about the regulation of growth of the GI tract, particularly the factors regulating tissue repair and regeneration by growth of new cells following injury. The gastrointestinal hormones may play a key role, but this remains to be demonstrated and proven.

Recent investigative work by an NIADDK grantee has described the interrelationships of various hormones in the regulation of growth in the gut and related organs. "Epidermal growth factor," for example, inhibits gastric acid secretion but increases DNA synthesis of the gastric gland mucosa (mucous membrane lining the stomach wall); this factor has no effect on duodenal and colonic mucosa. Pentagastrin, on the other hand, stimulates DNA synthesis in all three mucosae.

Of particular importance are the roles of the known gastrointestinal hormones, secretin and cholecystokinin. In addition to regulating the release of pancreatic secretions, these hormones also stimulate the growth of the exocrine pancreas. Gastrin has a similar effect. In the stomach, however, secretin alone does not stimulate cell growth and is shown to inhibit DNA synthesis.

A genetic marker for duodenal ulcers. The term duodenal ulcer embraces a diversified group of disorders sharing the common clinical manifestation of ulceration of the lining of the duodenum. The occurrence of duodenal ulcer in families does not appear to conform to standard inheritance patterns. Geneticists and gastroenterologists have long sought factors that would serve to explain the duodenal ulcer pattern and thus help to identify people at risk for this disease.

One such factor, pepsinogen I (PG I), a precursor of one form of the digestive enzyme pepsin, which is

secreted in the stomach, has repeatedly been found to be higher in patients with established duodenal ulcer. NIADDK grantees have found that in two families with a prominent history of duodenal ulcer, there is an abnormally high production of PG I, and this may be a marker for susceptibility to duodenal ulcer disease. Further studies are recommended to determine what additional markers of other physiological abnormalities in ulcer patients interact with environmental factors (such as stress) to translate genetic predisposition into clinical disease.

Advances in instrumentation. New advances in gastroenterology have been made by researchers using revolutionary fiberoptic and mechanical devices. One such instrument, the fiberoptic endoscope, is a flexible diagnostic tool used to examine areas previously inaccessible to the conventional rigid, tubular gastroscope. The fiberoptic endoscope has provided observations that may aid in the recognition and therapy of ulcers and other disorders of the digestive tract. Similarly, Institute-supported investigators have determined that the gastrocamera, which has come into wide use in Japan in recent years, is an accurate, well-tolerated, and safe endoscopic technique for patients with gastric ulcers. The gastrocamera has been found to be particularly useful for studying small ulcers not detectable by other procedures, and the use of the wide-angle view of its lens has been found to be advantageous in followup examinations to evaluate ulcer healing.

In the diagnosis of acute upper gastrointestinal bleeding, improvements in endoscopy have also been invaluable. For example, Institute grantees have demonstrated that the flexible fiberoptic endoscope provides a more detailed diagnostic picture than do conventional radiographic methods.

Control of upper gastrointestinal bleeding. Effective control of upper GI hemorrhage, such as occurs in bleeding ulcer, is a major problem. Surgery may require resection of a part of the stomach or section of nerves to the stomach. Other techniques being used and evaluated include electrocautery (searing of tissue), tissue adhesives, and mechanical clips. These techniques can be costly and difficult to apply, and they may produce complications. Investigators have developed a new method that appears promising and embodies relatively little risk. It involves directed spraying of blood-clotting factors, such as thrombin and a plasma concentrate of fibrinogen (cryoprecipitate), through a fiberoptic endoscope to form a firm fibrin clot at the site of GI bleeding and arrest the hemorrhage. Cryoprecipitate is superior to ordinary commercial fibrinogen in that it does not carry the risk of transmitting viral hepatitis. The internal spray technique, which was effectively used in a bleeding stomach ulcer model in dogs, now awaits further experimental application in patients.

Another study has shown that the internal use of the argon laser (through a flexible endoscope which is advanced to the bleeding spot in the upper GI tract) in conjunction with pressurized carbon dioxide to clear blood from the bleeding site appears promising for safe and effective control of massive bleeding. Data obtained from a clinical trial involving about 100 patients will serve as the basis for a larger multicenter trial.

Liver and bile disorders complicate ulcerative colitis. An Institute grantee has shown that hepatobiliary disorders (related to the liver and biliary tract) are the most common extracolonic complications accompanying ulcerative colitis and that these may be life-threatening. In a clinical study, 202 patients ages 1 to 86, admitted to a university hospital between 1966 and 1975 with a diagnosis of ulcerative colitis, were reviewed. Hepatobiliary status was evaluated on the basis of liver function tests, liver biopsy, and evidence of extrahepatic biliary disease. Liver function tests were classified as normal, mildly abnormal, and markedly abnormal. On this basis, 92 of the 202 patients with ulcerative colitis had normal liver function tests, 60 had mildly abnormal tests, and 50 had markedly abnormal tests. Markedly abnormal tests correlated positively with whole colon involvement and severity of ulcerative colitis.

Growth retardation and Crohn's disease. Crohn's disease is a chronic, progressive, grave inflammatory condition of the gut, most frequently located in the small intestine (the ileum). It causes severe abdominal pain, diarrhea, malnutrition, and, in some cases, death. Many patients have prolonged periods of hospitalization, and it is sometimes necessary to perform abdominal surgery, involving the removal of portions of the small intestine.

In a recently completed study, NIADDK grantees have successfully reversed growth retardation in a group of children with Crohn's disease. Seven children (ages 12 to 16) were evaluated. All of these patients had evidence of severe growth failure, as demonstrated in their height percentiles, which spanned from the normal range to less than the third percentile. The children were found to ingest only 43 to 62 percent of the total calories needed for normal growth. This is especially significant when the problems of general caloric deficit are superimposed on the excessive gastrointestinal protein loss and malabsorption caused by Crohn's disease.

Adequate calorie and protein intake by mouth was instituted once each child's intestinal symptoms were sufficiently controlled by use of medication or intravenous feeding. Eventually, caloric goals were set to meet recommended dietary allowances for age and sex. Reversal of impaired growth was achieved in each patient with therapy that emphasized oral nutritional supplementation.

Drugs shown effective in treating Crohn's disease. The results of a long-term clinical study organized by the Institute show that both prednisone and sulfasalazine, two anti-inflammatory drugs, are significantly better than a placebo in causing a remission of active Crohn's disease. Azathioprine (a third drug tested) was somewhat better than a placebo, but not enough to be statistically significant. None of the three drugs was better than a placebo in preventing flareups or recurrence

of the disease. The study also demonstrated that the combination of prednisone and sulfasalazine was less effective than prednisone alone for inducing remission.

In the course of screening more than 1,400 patients and studying more than 700 of them for periods of up to 2 years, the investigators were able to make other determinations about Crohn's disease. For example, the X-ray characteristics of the disease were carefully and exhaustively defined to aid radiologists in recognizing and following its course. In addition, the value of rectal biopsy in diagnosis was examined and found to be minimal. The response of Crohn's disease to surgery was also documented to aid surgeons in deciding when to operate on patients with the disease.

Quality of life improved after surgery for Crohn's disease. At any stage of Crohn's disease, patients are at risk of developing intestinal obstruction, abscesses, and fistulas (abnormal passages) as well as involvement of more distant organs. Although elective surgery has been the primary solution for such problems, the prospect of complications as a result of the surgery or recurrences of the disease after surgery may deter many physicians from attempting it.

In an effort to assess the impact of elective surgery for Crohn's disease on later lifestyle, gastroenterologists interviewed 51 patients who had undergone their first operation 5 to 10 years earlier. Despite the untoward influence of recurrent disease and supplemental ileostomy, 47 of the patients (92 percent) reported improvement in all areas surveyed: physical symptoms, interpersonal relations, performance at school and work, recreational pursuits, sex behavior, and perception of body image. Thus, these patients collectively viewed their operations as a source of long-term improvement in the quality of their daily living.

Viruses implicated in Crohn's disease. Research has provided additional evidence that strengthens the hypothesis that viruses may play a causative role in inflammatory bowel disease. An NIADDK grantee found that while viruses can be isolated from patients with Crohn's disease, ulcerative colitis, necrotizing enterocolitis, and colon carcinoma, those isolated from patients with Crohn's disease are unique and differ from the viruses associated with the other illnesses. In Crohn's disease, the presumed viral infection involves both the normal and abnormal bowel regions. Viruses derived from patients with Crohn's disease and ulcerative colitis could be isolated in four tissue culture systems and serially replicated up to 15 and 12 times, respectively. These agents, not found in normal control patients, develop in the cytoplasm (general cell contents as distinguished from the central nucleus) of infected cells and occur at times in crystalline-appearing aggregates.

If the virus etiology can be established, vaccines against Crohn's disease (and possibly ulcerative colitis) may be achievable. Antibodies prepared against the Crohn's disease-linked virus inhibited the growth of that agent but not of the others, and the antibody prepared against the ulcerative colitis isolate was likewise specific for that virus.

Immune mechanisms in inflammatory bowel disease. Evidence suggests that, regardless of the primary causative agent or factor in inflammatory bowel disease, certain immune processes in the body play a part in the persistence or chronicity of the disease. Among the immunologic disturbances found in patients with Crohn's disease or ulcerative colitis are high levels of antibodies to cells lining the intestine and the apparent cytotoxicity (cell-killing activity) of circulating lymphocytes (white blood cells) for these epithelial cells.

Certain cytotoxic white blood cells, called "natural killer cells," will spontaneously kill a variety of other living cells, a process that appears to be mediated by receptors on the surface of the killer cells. Recent studies indicate that natural lectins—cell membrane molecules composed of sugars and proteins—may play a key role in allowing the white cells to recognize and kill other cells. Experiments have revealed that these sugars are able to inhibit the action of killer cells, possibly by binding to their surface receptors. By using these sugars as probes, Institute scientists hope to gain new understanding of the killing process, the cells that mediate killing, the mechanisms involved, and how to control the destruction of healthy body cells, specifically those lining the intestine.

Role of bacterial toxin in relapse of inflammatory bowel disease. Recent studies have incriminated the bacterium **Clostridium difficile** and its secretory products as responsible for the destruction of cells in the mucous lining of the colon following antibiotic therapy for colitis. For the first time, investigators have found this bacterium and its toxin in patients during symptomatic relapse of inflammatory bowel disease and diarrhea not necessarily related to antibiotic therapy. Most of the patients studied improved after oral administration of the antibiotic drug vancomycin.

Results indicate that the clostridium toxin elaborated by these bacteria exacerbates relapses of inflammatory bowel disease, irrespective of previous antibiotic therapy. Inasmuch as the presence of the bacterium and its toxin in healthy newborns suggests that clostridium belongs to the normal bacterial makeup of the intestine, its conversion to a destructive agent in the adult colon could be due to a disturbance of the balanced microbial populations in the gut. Whatever causes inflammation of the large bowel may be responsible for such a disturbance, resulting in abnormal colonization by clostridium and toxic damage to the mucous membrane.

Development of an "artificial gut" system. A decade ago, Institute grantees provided a new and exciting treatment for victims of certain bowel diseases. A permanently implanted plastic, exteriorized arteriovenous shunt (a means of access to the circulatory system),

which had originally been devised for use by artificial kidney patients, was applied as an "artificial gut" system that can provide continued nutrition to patients who lack effective bowel function. In previous attempts at providing complete nutrition to patients by infusion of sterile nutrient solutions via conventional needles, it was found that the blood vessels involved soon became damaged and scarred by these concentrated solutions. Now, however, solutions that contain all needed nutrients can be infused into the plastic shunt of the patient, where they mix readily and safely with an excess of circulatory blood, without causing damage to blood vessels. Moreover, with use of this procedure, patients who have lost their bowel function temporarily or permanently because of disease or surgery (such as that performed to remove cancerous portions of the intestine) can now continue living.

Other surgeon-investigators have developed a "stomach patch" technique for the surgical repair of the opening between the stomach and esophagus in patients with acid peptic stricture of the esophagus, achalasia (failure of the esophageal muscles to relax during swallowing), and hiatus hernia.

Insights into milk intolerance and Kepone poisoning. It was during the past two decades that scientists traced the cause of a specific type of milk intolerance in certain otherwise normal adults and in some patients with inflammatory bowel disease to a deficiency in the intestinal enzyme lactase, which converts lactose ("milk sugar") into its simple sugar components, glucose and galactose. Subsequently, other NIADDK grantees showed that this condition is very common among black and Oriental adults, at first suggesting a genetic etiology for lactase deficiencies in a large part of the world's nonwhite adult population. They have since demonstrated that lactase deficiency, with painful intestinal symptoms following ingestion of more than 4 to 8 ounces of milk (or the equivalent in the form of milk products), is found in adults from populations that do not traditionally raise milk-producing animals. This discovery provides a rational cause for a multitude of previously unexplainable chronic gastrointestinal complaints among black and Oriental adults who follow Western-style eating habits, which in some cases has led to unnecessary (and sometimes repeated) exploratory abdominal surgery.

Other Institute grantees have demonstrated that a special resin (cholestyramine) binds the poison Kepone in the intestine and increases its rate of removal from the body. This discovery was applied successfully in the treatment of a case of multiple chronic human poisoning by Kepone in Virginia (through industrial exposure) with the gradual removal of the substance, which tends to accumulate in fatty tissues.

Prostaglandin protection in pancreatitis. Prostaglandins have been noted to have a protective effect against various types of injury to the gastrointestinal mucous lining. For the first time, investigators have reported possible protective effects of these compounds on other injured tissues.

Acute experimental pancreatitis (inflammation of the pancreas) was induced in mice by means of a diet deficient in choline, a vitamin-like substance essential to liver function, and rich in ethionine, a nonbiological analogue of methionine, a sulfur-containing essential amino acid. Administration of prostaglandin E_2 1 hour before and 4 hours after institution of the experimental diet lowered the mortality rate for diet-induced pancreatitis from 56 to 31 percent. Prostaglandin E_2 improved other indices for the disease as well. Although the basis for the protective effect of prostaglandin E_2 remains unclear, these observations suggest that the compound may act to reduce the alteration in membrane integrity that occurs during experimental diet-induced pancreatitis.

Surgery-drug combination effective against Zollinger-Ellison syndrome. Patients with the Zollinger-Ellison syndrome (ZES) suffer from tumors of cells in the pancreatic islet tissues, intractable peptic ulcers, and excessive secretion of stomach acid. These tumors produce excessive amounts of the hormone gastrin, which stimulates the constant and excessive secretion of gastric acid by the stomach. Although such patients have been managed either surgically by total gastrectomy, which obviously eliminates the peptic ulcers, or medically by the drug cimetidine, which suppresses gastric hyperacidity, both of these modalities have distinct limitations. Whereas total gastrectomy carries the risks of surgical mortality, malabsorption, malnutrition, or other postoperative complications, cimetidine treatment does not adequately control ulcer disease, and it precludes the possibility of surgical cure afforded by removal of pancreatic islet cell tumors. In an effort to overcome these limitations, clinicians evaluated the effects of vagotomy (cutting the nerve supply to the gastric glands) in combination with cimetidine on stomach acid secretion and the clinical course of ZES patients. Preliminary results indicate that this combination may be safer than total gastrectomy and may curb excess acid secretion to a greater extent than either modality can alone. Discovery and removal of pancreatic islet cell tumors during the operation could lead to complete cures for approximately 10 percent of ZES patients.

In another NIADDK study, scientists have found that combined administration of cimetidine and the anticholinergic drug isopropamide, which blocks the transmission of nerve impulses, is more effective than use of either drug alone. The combined therapy could be less expensive and require lower doses. Additional clinical experience is needed to clarify whether long-term usage of this therapy can obviate the need for gastrectomy.

Improved diagnosis for malabsorption disease. Patients with the disorder called nontropical sprue have poor intestinal absorption and excessive elimination of unabsorbed dietary substances following ingestion of gluten-containing foods such as wheat, rye, oats, and

barley. An associated feature of this "gluten enteropathy" is a lesion of the small bowel (flattening and erosion of the mucosa). Since such lesions may result from other gastrointestinal disorders, such as chronic infantile diarrhea and cow's milk allergy, a series of three intestinal biopsies has been necessary in some cases for a correct diagnosis. NIADDK grantees are attempting to simplify the diagnosis in order to avoid repeated biopsies. They have found that a statistical analysis of the activity of alkaline phosphatase from the small bowel, observed in a gluten-containing organ culture of small portions of the small intestine, reliably differentiates gluten enteropathy sprue from other causes of the small bowel lesion. This finding avoids the risk of numerous biopsies and allows prompt pursuit of alternative diagnoses when there is no indication of gluten sensitivity.

Drug therapy for short bowel syndrome. The short bowel syndrome is characterized by intestinal malabsorption of nutrients, excess fat in the stool, diarrhea, depletion of fluid and electrolytes, acid-base imbalance, and massive weight loss. It usually follows surgical removal of an extensive section of small intestine, with consequent excessive acid burden from the stomach, proportional to the length of intestine removed. Of critical importance for the survival of patients in such a situation is the absorptive efficiency of the intestinal remnant.

Since the heavy load of stomach acid entering the remnant of the small intestine might hinder digestion and absorption of foodstuffs in such patients, or even cause peptic ulceration, medical intervention is necessary. NIADDK grantees have demonstrated that the drug cimetidine significantly improves digestion and corrects diarrhea, nutrient malabsorption, and other abnormalities of patients with short bowel syndrome. Cimetidine dramatically reduces the acidity and volume of gastric juice entering the duodenum, and the researchers recommend that its use become standard additional therapy for other patients with short bowel syndrome who are similarly affected by relatively excessive loads of stomach acid.

LIVER AND BILIARY TRACT DISEASES

Through its liver and biliary tract diseases program, NIADDK supports studies of the structure, function, and diseases of the liver, biliary tract, and gallbladder. Included are inflammatory, metabolic, and genetic diseases of the liver, such as hepatitis, cirrhosis, Wilson's disease, primary biliary cirrhosis, fatty liver, hepatic encephalopathy, Dubin-Johnson syndrome, and Gilbert's disease. Other investigations focus on liver regeneration, liver assist devices, and liver transplantation, as well as liver ischemia, portal hypertension, and toxic liver disorders. Biliary and gallbladder studies are directed at cholestasis, pigment and cholesterol gallstones, and the metabolism of bile and bile salts.

Following the discovery that secretion of hepatic bile of an abnormal composition (high-cholesterol, low-bile salt) underlies the generation of cholesterol gallstones, investigators reported for the first time a decade ago that long-term oral administration of a natural bile acid (chenodeoxycholic acid) can dissolve long-standing cholesterol gallstones, the most common type of gallstone. In related studies, scientists devised a method of measuring the lipid composition of human bile under physiologic conditions in man. This procedure has been proven useful in determining the effects of various diets, drugs, and diseases on the metabolism of biliary lipids in man and has been particularly applicable to the study of cholesterol gallstone formation.

Following recognition in the 1960s of the virus responsible for serum hepatitis (hepatitis B)—the so-called Australia antigen—Institute scientists developed a practical, sensitive test for screening blood donors and blood products. This advance sharply reduced what at one time was a prevalent risk of transmitting hepatitis by transfusion of blood containing viable hepatitis virus. By obtaining evidence to indicate that Australia antigen is part of the hepatitis virus, NIADDK scientists helped provide the first step toward the development of an antihepatitis vaccine or a therapeutically effective antibody preparation against Australia antigen. They also provided evidence that fatal liver necrosis or cirrhosis occurs only in those cases of acute viral hepatitis in which the antigen is present.

During the past decade, Institute grantees induced alcoholic hepatitis in baboons by giving them alcohol in combination with a nutritionally adequate diet. In man, alcoholic hepatitis and fatty liver precede alcoholic cirrhosis (scarring of the liver), and it was significant that the experimental animals also eventually developed cirrhosis. The researchers have also produced evidence suggesting that alcohol consumed by chronic drinkers might have a direct injurious effect on cells of the small intestine strikingly similar to the damage to liver cells that often occurs in alcoholic people. Such damage was demonstrated even in nondrinkers after exposure to relatively limited periods of alcohol intake.

To assist in development of an "artificial liver" device to support patients temporarily during life-threatening episodes of acute liver failure, NIADDK scientists have used techniques such as affinity chromatography to remove accumulating bilirubin and other protein-bound substances from plasma and blood. Another approach has been the development of a hollow fiber device for growing rat liver tumor cells capable of metabolizing bilirubin in the blood of such patients as it is being passed through the device. The goal of this line of research is to assist patients with liver failure, those with an intoxication by protein-bound drugs, or those with specific metabolic defects.

More than a decade ago, NIADDK-supported investigators reported the first successful liver transplantations in four children. The livers remained functional for periods up to 1 year, a success that was credited to a combination of improved methods of immunosuppression, organ treatment and storage, tissue typing and organ-recipient matching, and surgical technique. Research continues toward establishing the exceedingly difficult procedure of liver transplantation as a practical therapeutic procedure.

Highlights of Recent Advances

The selections below highlight some of the most recent advances against liver and biliary tract diseases

- Researchers have discovered a postsurgical solvent for cholesterol gallstones monooctanoin Experiments with this agent have shown it to be an effective therapeutic option for removing cholesterol gallstones or gravel remaining in patients after gallbladder surgery
- For the first time, a hepatitis virus, that causing hepatitis B, has been isolated, and a vaccine against it has been tested and found effective This development represents a further advance on the discovery within the last few years that three different types of viruses are responsible for hepatitis
- By using aspirin to inhibit hypersecretion of mucus, Institute grantees have prevented cholesterol gallstone formation in the presence of supersaturated bile in an animal model
- More effective methods of immunosuppression, including use of the drug cyclosporin A have shown promise in liver transplants
- An NIADDK grantee by using recombinant DNA techniques, has increased the sensitivity for detecting hepatitis B viral DNA sequences in liver tissue about 1,000 times over the previously most sensitive technique of radioimmunoassay
- Institute-supported research has elucidated at the molecular level the mechanism whereby phototherapy corrects neonatal jaundice

Pathways of Research Progress

Emulsifier shown effective in dissolving residual gallstones. A recurring postoperative complication in patients who undergo cholecystectomy (surgical removal of the gallbladder) is the persistence of residual cholesterol gallstones or their fragments in the bile ducts. Some of these stones lend themselves to mechanical extraction by passage of a catheter with a tiny basket at its tip or by enlargement of the opening at the lower end of the bile duct, but firmly impacted stones are extremely difficult or impossible to dislodge. Further, therapeutic local infusion of bile salts such as cholate not only takes exceedingly long to dissolve the stones, but has caused severe inflammation and death in animals. Accordingly, investigators have been screening a number of agents to find one that will efficiently and safely dissolve cholesterol gallstones in humans.

In recent studies, investigators have reported some success with monooctanoin—a commercial emulsifier derived from digested fat and widely used to treat patients with impaired intestinal absorption of nutrients. In test tubes, the agent dissolved cholesterol stones more than twice as fast as bile salt solutions did, and during 4 to 21 days' infusion into 10 of 12 postcholecystectomy patients, it caused either rapid shrinkage or complete disappearance of stones remaining in the bile ducts. Thus, monooctanoin appears to be a therapeutic option for fast postoperative removal of residual gallstones and stone fragments. It also appears likely that collaboration of hepatologists and pharmaceutical chemists in this decade will lead to the identification of superior solvents that will dissolve cholesterol gallstones still more rapidly than monooctanoin and be tolerated just as well.

Ultrasonic properties of gallstones. Although ultrasonographic examination of the gallbladder has been accepted as a reliable indicator of the presence of stones, the unequivocal diagnosis of gallstones depends on gallbladder echoes accompanied by acoustic shadows directly behind the stones. When either internal echoes or acoustic shadows occur alone, the ultrasonic diagnosis of gallstones is less certain.

NIADDK grantees have studied the effects of gallstone size and chemical composition on ultrasound appearance. The researchers found that all stones larger than 4 mm in diameter produced a distinct sonic shadow. Gallbladder "sludge" produced internal echoes without a sonic shadow. Four of seven cholesterol stones containing 88 percent cholesterol floated and produced a sonic shadow without internal echoes. This last feature may identify patients who are good candidates for gallstone dissolution with chenodeoxycholic acid rather than surgical intervention.

Gallstone formation in Pima Indians. The prevalence of cholesterol gallstones among postpubescent Pima Indians is higher in female than in male members of the tribe. Since gallstones arise from precipitation of cholesterol in saturated bile, the state of cholesterol saturation may exist since birth because of an inherited defect in lipid metabolism, or may be the result of an increase in lipids taking place toward the onset of puberty. NIADDK scientists undertook to resolve this question by measuring bile composition and bile acid pool size in healthy Pima youths of both sexes.

It has been found that high cholesterol saturation of bile is a general characteristic of Pima Indians and that levels increase significantly in both sexes during and after puberty. This increase in saturation is correlated with obesity and, under the influence of estrogens (female sex hormones) and failure of the bile acid pool size to expand with age, leads to a higher prevalence of gallstones in women several years later after one or more pregnancies.

Mechanisms and prevention of cholesterol crystal formation. The finding that most patients with cholesterol gallstones had bile in which the cholesterol existed in a supersaturated solution led to increased research in the area, including the development of bile acids that can dissolve gallstones. However, the later finding that some individuals with no gallstones also had bile supersaturated with cholesterol implicated additional

factors in the formation of gallstones. A nucleation (formation of a crystal) step that causes the cholesterol to come out of solution has long been considered critical, but the nucleating materials had not been identified.

Now NIADDK grantees have used an animal model in which cholesterol gallstones develop quickly and with regularity to show that high doses of aspirin can prevent gallstone formation both **in vivo** and **in vitro**. It appears that the aspirin inhibits mucus hypersecretion by the gallbladder (while exerting no effect on bile supersaturation). The gallbladder acts as a storage vessel for the cholesterol supersaturated bile; its mucus may serve as a nucleation matrix for cholesterol gallstones.

This finding points to the possibility of discovering a simple, safe, and inexpensive drug that could prevent the formation of gallstones in populations at high risk to develop them, such as young Indian women and other women over 40.

Gallbladder function and gallstone formation during pregnancy. Previous studies have established that cholesterol gallstones are more prevalent among women than among men, especially during pregnancy and periods of medication with contraceptive steroids. However, the biliary tract mechanisms underlying this sex difference remain obscure. Nearly 50 years ago, X-rays revealed enlargement and impaired emptying of gallbladders in women during the latter part of pregnancy, and such findings have since been observed in certain laboratory animals and have been reproduced in other animals by administration of ovarian steroid hormones (such as estrogen and progesterone) known to be increased during the course of pregnancy. Recently, scientists have reported on a study undertaken to determine whether the pregnant state and/or contraceptive steroids, which consist of combinations of estrogens and progestational hormones, alter gallbladder function in a manner that produces gallstones.

Using the sophisticated technique of ultrasonography to measure gallbladder size during pregnancy, the investigators found the volume of bile in this organ to be significantly increased and its emptying rate decreased, thus setting the stage for crystallization of cholesterol from supersaturated bile and subsequent gallstone formation. These abnormalities were probably influenced by high levels of estrogen and progesterone as well as increased water content of the gallbladder and a diminished bile acid pool. Such findings strengthen the view that pregnancy increases the risk of cholesterol gallstones by impairment of gallbladder function, but they provide no evidence that contraceptive steroid medication also promotes stone formation by interference with this organ.

Advances in dissolving cholesterol gallstones. Oral administration of chenodeoxycholic acid (CDCA) appears to decrease cholesterol synthesis in the liver and causes decreased cholesterol secretion in bile. Experiments have shown that CDCA taken orally frequently results in dissolution of existing cholesterol gallstones. The National Cooperative Gallstone Study, supported for the past several years by NIADDK, has 10 centers across the country treating about 1,000 gallstone patients with oral administration of CDCA. Final results of the study are being prepared.

Preliminary clinical data suggest that dissolution therapy might be appropriate for selected patients with cholesterol gallstones. Some of the problems encountered are recurrence of stones after treatment is discontinued, resistance to treatment by obese patients, the need for 2 or 3 years of treatment for total dissolution of existing gallstones, especially large ones, and the lack of response in some patients. The most frequently encountered side effect of CDCA is diarrhea, which disappears or is minimal when the dosage is lowered. Other Institute studies have shown that CDCA given to obese persons undergoing weight reduction will reduce bile saturation with cholesterol (a condition essential for the generation of cholesterol gallstones) and could protect against gallstone formation.

In related work, Institute grantees have recently been successful in developing a new hamster model of gallstone formation even more closely approximating the human situation. The model was developed through the feeding of female Syrian golden hamsters with an increased cholesterol diet, alone or in combination with a dose of ethinyl estradiol (a synthetic estrogen) within the range currently used in oral contraceptives. The oral administration of chenodeoxycholic acid and ursodeoxycholic acid prevented gallstone formation via mechanisms resembling those reported for patients but is yet to be tested for the curative action of dissolving gallstones in this model.

Hepatitis viruses elucidated. Studies of acute hepatitis in chimpanzees and in patients who have had blood transfusions have suggested the existence of a transmissible viral agent serologically distinct from the hitherto recognized hepatitis viruses A and B. Although not yet found in association with inflammatory liver disease, the presumed infectious agent has been conveniently designated "non-A, non-B hepatitis virus." In a group of 388 patients followed prospectively for at least 9 months at the NIH Clinical Center, 26 developed acute non-A, non-B posttransfusion hepatitis. The diagnosis of acute hepatitis in 12 of these 26 subjects was based on elevated levels of serum transaminase, an enzyme found especially in the liver, that persisted for more than 1 year.

Liver biopsy of the 12 chronic liver disease patients established chronic active hepatitis bordering on cirrhosis in 6 patients, and milder chronic persistent hepatitis in 2 patients. The abnormally high serum transaminase levels returned to normal after 1 to 3 years in all of the patients, thus suggesting a better prognosis for this disease than for chronic active hepatitis of other causes. The development of a reliable blood test for definitive identification of the non-A, non-B agent as a virus could lead to production of a vaccine for prevention of this form of posttransfusion hepatitis.

Phototherapy and neonatal jaundice. The enzymatic ability to conjugate (chemically join together) the bile pigment bilirubin with certain sugar components is not fully developed at birth, and because unconjugated bilirubin, produced in the liver, cannot be excreted into the bile, it backs up into the blood, causing jaundice. Exposure to light rays of various concentrations (phototherapy) is used to correct jaundice in newborn infants. Its action at a molecular level has not been previously characterized.

It now appears, from investigations by NIADDK-supported scientists, that phototherapy works by converting the rigid, highly hydrogen-bonded isomer of bilirubin, which cannot be excreted into bile without conjugation, into a labile form in which the hydrogen bonds are broken. This form can be secreted by the liver into the bile without conjugation. Once in the bile, it reverts back to its rigid form and is not reabsorbed in the intestine; thus, the net effect is that unconjugated bilirubin is excreted into the intestine and leaves the body with the feces. Future studies may indicate other modalities that can cause the same structural change in bilirubin.

New therapeutic approach for porphyria. Porphyrias constitute a group of disorders in which an excess of porphyrins and their by-products accumulate in the blood and tissues. (Porphyrins are normally contained in many cells of the human body, and a purple red porphyrin, heme, is the basis of hemoglobin and the red color of blood.) Hepatic porphyria, transmitted genetically, is a common form of the disorder. It is characterized by overproduction of porphyrin in the liver and by acute attacks of abdominal pain and neurological dysfunctions such as paralysis of limbs and profound mental distress. NIADDK grantees have found that heme infusions can block the progress of attacks of hepatic porphyria in a drug-induced experimental model.

The researchers discovered and identified a green pigment found in the liver after administration of a drug, allyl isopropylacetamine (AIA), which caused porphyria. A porphyrin-containing liver enzyme, cytochrome P-450, breaks down this drug but in so doing is itself destroyed. The lack of enzyme allows the liver to overproduce the porphyrins, setting off the acute attack. This can be inhibited by an infusion of heme, which is converted by the liver into cytochrome P-450 and thus stops the abnormal overproduction of porphyrins and the attacks. It is anticipated that heme infusion may also enhance biotransformation of other drugs that inactivate or consume cytochrome P-450, and it therefore may be useful for therapy in hepatic porphyria.

Drug therapy of acute hepatic failure. Although hydrocortisone has been used since 1951 in acute hepatic failure caused by drugs or viruses, its effectiveness had not been evaluated. Therefore, the Institute performed a 4-year randomized, controlled clinical trial of corticosteroid therapy in liver failure at research facilities through the United States and Canada. The cooperative study showed neither benefit nor harm from hydrocortisone, but an incidental finding provided a clue to the discrepancies among previous, unblinded studies. Thirty-five percent of patients survived when the cause of liver disease was one of the two known hepatitis viruses (A or B), whereas only 7 percent survived when the cause was a non-A, non-B virus or a drug. The marked effect that hepatitis etiology has on survival, therefore, must be taken into account before conclusions are drawn about the influence of hydrocortisone therapies.

Sensitive test for chronic liver disease. Only a small percentage of patients who have an acute attack of viral hepatitis go on to develop chronic liver disease, cirrhosis, and possibly even liver cancer. Current tests for viral antigens and antibodies in the serum or liver, as well as studies of liver structure, have been unable to distinguish those who will be likely to develop chronic disease.

Scientists have now increased the sensitivity of a test for detecting persistence in tissues of viral particles by 1,000 times over the previously most sensitive technique of radioimmunoassay, thereby greatly increasing the possibility of detecting the persistence of the virus in the liver. This feat has been accomplished by the use of the newest techniques in molecular biology—cloning of the hepatitis B virus and direct examination of small samples of the liver for the presence of viral DNA, which can be detected even if the virus is not being produced in the liver.

Early detection and control of alcoholic liver injury. Cirrhosis of the liver as a complication accounts for 75 percent of all deaths attributable to alcoholism and, since 1978, is the fifth leading cause of death from disease nationwide. In recent years, many studies have shown that alcohol exerts a direct toxic action on the liver. Many alcoholics, however, do not develop cirrhosis, and the factors producing susceptibility remain unidentified. Early detection of heavy drinkers particularly prone to become alcoholics might allow for effective therapeutic intervention prior to mental or physical deterioration or development of alcoholic cirrhosis.

Scientists have now developed an approach for reducing the incidence of alcoholic liver disease. It is based on a better definition of the susceptible population, early detection by the use of biochemical markers of alcoholism, improved blood enzyme tests for liver cell death, and further pharmacologic and toxicologic studies aimed at successful therapeutic interference with the effects of alcohol on the liver. The investigators note that their strategy will not prevent alcoholism, for it is not designed to induce people to curb their drinking habits. However, it would identify subgroups prone to develop alcoholic liver disease and conceivably may lead to significant reduction in incidence, morbidity, and mortality.

Improved prospects for liver transplants. The outlook appears to be brightening for liver transplant patients as surgical and technical improvements lead to

gradual increases in their survival rate. Since the first liver transplantations in 4 children in the 1960s by Institute grantees, the investigative team's 15-year series now totals 141 liver grant recipients, of whom 46 survived 1 year or more. In this group are a 13-year-old girl who sets the record for survival (9 years) and a liver graft recipient who now has a 2-year-old child. She is the only known liver transplant recipient to bear a child. The team now achieves at least 1-year survival for half the transplant patients. Of the group's last 30 patients, who underwent surgery between August 1976 and December 1977, 13 were alive 2-1/2 years later. Two others died after a year.

Of the total 141 liver transplant patients, 48 underwent the procedure because of biliary atresia, 36 for chronic aggressive hepatitis, 19 for primary liver malignancy, and 15 for alcoholic cirrhosis. Investigators believe that improved drug control of graft rejection will improve transplant results; they cited a new immunosuppressive drug, cyclosporin A, as an example. This fungus extract-derived substance has shown excellent results in skin and organ transplants in experimental animals and has been used in clinical trials of liver and kidney transplants in England, and more recently in the United States.

Program Accomplishments—National Digestive Diseases Education and Information Clearinghouse

As a major information service of NIADDK, the National Digestive Diseases Education and Information Clearinghouse acts as the coordinator of a national effort to educate the public, patients, their families, physicians, and other health care providers about the prevention and management of digestive diseases.

The clearinghouse provides a central point for the exchange of information among professional organizations, foundations, and voluntary health organizations involved with digestive health and diseases. In working with these groups, the responsibility of the clearinghouse is to aid the distribution of available materials, determine what informational and educational materials are needed, and encourage production of such materials.

In January 1979, the National Commission on Digestive Diseases made its report to Congress. The first recommendation was to establish the National Digestive Diseases Education and Information Clearinghouse under NIADDK (then NIAMDD), and specific functions for the clearinghouse were outlined.

The clearinghouse has been operating under contract from the Institute since June 1980. Activities and goals of the clearinghouse are based on input from digestive diseases organizations and broad consultation with other pertinent groups. A standing advisory committee of representatives from these groups has been formed.

Clearinghouse publications consist of fact sheets and "Letter from the Clearinghouse" developed by a previously existing digestive diseases information center (which had been operating on a 2-year grant from a drug company). Fact sheets describe specific disease areas and are prepared by professionals in the field at the request of the clearinghouse committee. From meetings of the advisory committee subgroups, new fact sheets were initiated, reviewed, and/or produced, including cirrhosis of the liver, diarrhea from infectious causes, heartburn, and milk intolerance. Future topics for inclusion are gallstones, stomach ulcers, bleeding in the gut, and others to be determined. "Letter from the Clearinghouse" discusses current research advances and actions of various government bodies and voluntary and professional organizations.

The clearinghouse has also prepared a directory of organizations concerned with digestive diseases and provides an inquiry and referral service that responds to professional and public requests for information.

NUTRITION

NIADDK supports a broad range of nutrition research, the goals of which are to increase knowledge and understanding of the factors involved in normal nutrition and conditions involving nutritional deficiency, as well as to help the possible influence of nutrition in various health problems. Basic, clinical, and behavioral studies stress research on obesity with emphasis on prevention and control; supportive nutrition for hospitalized patients; nutritional therapy in pertinent diseases; human nutritional requirements and factors that influence these requirements; new technologies in the study of the function of nutrients; iron deficiency; metabolic roles of trace minerals; dietary fiber; interaction of nutrients; and the influence of nutrition on immune competence.

Obesity is the common form of malnutrition in the United States, reaching a peak in prevalence of 39 percent in men and 50 percent in women over age 30 (those persons 10 percent overweight or more). The etiology of obesity in most individuals is not known, but its association with other serious chronic conditions (especially diabetes mellitus, hypertension, gallbladder disease, and osteoarthritis) gives it major public health significance.

Institute-supported scientists have established that an excessive intake of calories is not necessarily the only cause of obesity. Other factors, many as yet unknown, may be involved, at least in a minority of obese persons. Among these are abnormalities in appetite regulation, metabolism, and hormone activity (in a very small percentage of cases) and, in selected cases, hereditary factors. The relationship of obesity to other diseases is also a focus of NIADDK research. Studies have shown that obese persons, who are generally more predisposed to gallstones than other persons, are even more susceptible during a period of active weight reduction. These patients are advised, therefore, to avoid a lifelong "see-saw" pattern of alternatively losing and regaining weight.

Another critical nutrition-related public health problem is the relationship of diet to overall lifespan and the

development of chronic degenerative diseases, particularly hardening of the arteries. Although overt vitamin or mineral deficiencies are no longer a major public health problem in the United States, the specific roles played in the body by the various micronutrients and macronutrients are an important aspect of NIADDK research. For example, Institute scientists discovered the essential nature of an additional mineral element, selenium, for the normal functioning of mammalian tissues.

Related studies have contributed vastly to our current knowledge of vitamin E and its role in body functions and have closed many gaps in existing knowledge about folic acid and other vitamins and their respective metabolic roles. For example, Institute scientists found that the presence of folic acid is essential for the formation of specific nucleoproteins, without which the natural maturation of developing red blood cells is arrested, resulting in anemia.

Institute scientists and grantees have also been pioneers in the development of gnotobiotic (germ-free) animals, equipment, and techniques. These investigations have made valuable contributions to existing knowledge concerning the intestinal microflora in humans and their effect on vitamin supply and nutrition-related metabolism. Other scientists supported by the Institute are actively studying the influence of food intake on metabolic pathways and body composition.

Highlights of Recent Advances

The following paragraphs present noteworthy recent accomplishments in the study of nutrition.

- Institute-supported research has shown that brown fat cells may be important sites of free energy production in the non-obese.
- Research sponsored by the Institute supports the concept that a decrease in number of insulin receptors on target cells (especially fat cells) is the principal cause of overall insulin resistance in human obesity.
- Findings by NIADDK grantees suggest that patients with anorexia nervosa have increased sensitivity to insulin, and that abnormal insulin binding to receptors in this disease may be corrected by restoring normal food intake and body weight.
- NIADDK grantees have found that certain keto acid analogues of branched-chain amino acids may offer new approaches to the nutritional treatment of patients with end-stage renal disease.

Pathways of Research Progress

Insulin receptors and obesity. Previous studies of animals and humans have suggested that there is a causal relationship between decreased insulin receptors on the outer membrane of fat tissue cells and the insulin resistance characteristic of obesity. In recent studies, Institute grantees have found a 40 percent decrease in insulin binding sites on isolated fat cells from obese subjects. They have also demonstrated that the insulin resistance of obese subjects is overcome when maximal plasma insulin levels normalize blood sugar. These findings lend further support to the concept that a decrease in the number of insulin receptors on target cells may be a principal cause of overall insulin resistance in human obesity.

Brown fat cells as sites of free energy in the non-obese. In recent studies, a number of investigators have emphasized differences in heat production (thermogenesis) as a factor in obesity. Recently it has been observed that a primary site of free energy production is in the brown adipocytes (fat cells), or "brown fat," in contrast to the regular yellow fat that predominates in mammals. Brown fat cells are very rich in mitochondria, the principal "energy factories" in cells, and appear to burn fat to produce free heat rather than to produce stored energy (fat). Cold exposure markedly increases brown fat, and hibernating animals have greater brown fat stores.

Rats that are allowed to eat according to their desire (rather than on a schedule) have more brown fat and are leaner than meal-fed rats. In humans, infrared photography has revealed brown fat areas on the back of the neck and down the center of the back and chest. The hormone norepinephrine stimulates thermogenesis in brown fat. These findings begin to hint that with a better knowledge of the effect of diet, exercise, environment, and norepinephrine-stimulating drugs on thermogenesis, a new understanding of the obesity or leanness of an individual based on enhanced thermogenesis by brown fat and of the extent of its occurrence in individuals may be within reach.

Increased binding of insulin to red blood cells in anorexia nervosa. Persons with anorexia nervosa have psychiatric and behavioral abnormalities, extreme loss of appetite, eventual emaciation, marked abnormalities of endocrine functions, and, in many cases, death from starvation. Institute grantees have studied insulin binding to red and white cells of patients with anorexia nervosa before and after nutritional rehabilitation. They have found that patients with anorexia nervosa have increased sensitivity to insulin, with an increased number of insulin receptors on outer cell membranes. The increase in the number of insulin receptors among the emaciated study group is the opposite of what happens in reverse nutritional states, such as overeating and obesity, where hormone receptor concentration is reduced. Abnormal insulin binding to receptors in anorexia nervosa may be corrected by restoration of normal food intake and body weight.

Role of vitamins, minerals, and diet in the body. Intramural and extramural NIADDK investigators have reported recently on a wide variety of studies aimed at elucidating the role of nutrition in normal body functions and in disease. Some of these results are summarized in the following paragraphs.

- A number of studies have continued to elucidate the role of zinc in the diet. For example, zinc supplementation in young children from low-income families significantly increased skeletal growth and appetite. Other research suggests that zinc from human milk is about two to four times more biologically available than zinc from cow's milk. Studies of adult men have shown that zinc loss in sweat increases with an increase in ambient temperature, and zinc has also been shown to be necessary for normal mobilization of vitamin A from the liver and for adequate immune function.

- Ingestion of large amounts of vitamin E caused no harmful effects but, when ingested in amounts exceeding what the body can absorb, the vitamin was lost from the body primarily through fecal excretion; blood levels of vitamin E could not be related to any consistent beneficial effect.

- In carefully monitored studies, low copper levels were observed in volunteers receiving supplemental zinc daily. This observation suggests that the ratio of certain minerals in the diet may have practical significance, especially in that zinc supplementation may suppress intestinal copper uptake and may thus increase the need for dietary copper.

- Research suggests that high-carbohydrate, high-fiber diets may be the dietary therapy of choice for patients with noninsulin-dependent maturity-onset-type diabetes mellitus and may have distinct benefit for patients with hyperlipidemia (excess fats or lipids in the blood). Long-term studies showed that diets containing 50 g of plant "fiber" per day are well tolerated and show no adverse nutritional effects but result in decreased blood sugar levels in such patients.

- Investigations have found that certain amino acid salts of branched-chain keto acids are relatively pleasant-tasting and more soluble than the unpleasant-tasting sodium or calcium salts of these compounds (the only ones heretofore available). These have been more effective for increasing nitrogen retention than equal amounts of amino acids in the dietary treatment of end-stage renal disease.

- Studies have shown that monkeys fed low-protein diets during the last four-fifths of pregnancy gave birth to infants equivalent in every respect to those born to mothers fed diets rich in protein. No adverse effects were observed on the mother or later in the life of the progeny, suggesting that the pregnant monkey is able to adapt considerably, presumably by improving metabolic efficiency. Since deliberate experimentation of this type in humans cannot be done, these studies have great value for extrapolation of human conditions.

- An NIADDK grantee has standardized model systems for evaluating the effects of dietary fiber on intestinal transit time, fecal enzymology, and the bioavailability of micronutrients. The investigator has firmly established a vitamin B_{12}-depleting effect of pectin.

Program Accomplishments—Clinical Nutrition Research Units

In a joint effort with the National Cancer Institute and the National Institute on Aging, NIADDK has fostered the development and operation of clinical nutrition research units to encourage a multidisciplinary approach to clinical nutrition opportunities and problems. A CNRU is an integrated array of research, educational, and service activities oriented toward human nutrition in health and disease. Core grants provided through the program are designed to provide a focus for clinical nutrition research and related activities in biomedical institutions and to complement ongoing research project grants and training awards.

The CNRU program represents an innovative approach for the stimulation of high-quality research in areas such as nutritional health maintenance, improved nutritional support of the acutely and chronically ill, nutritional support of the hospitalized patient, assessment of nutritional status, effects of disease states on nutritional needs, and effects of changes in nutritional status on disease. An appropriate environment is provided for the education of medical students, residents, practicing physicians, and trainees and fellows in nutrition. Each CNRU also provides support for a new investigator in clinical nutrition.

At a minimum, a CNRU must comprise seven components: research with human subjects and populations; laboratory investigation; research training; shared facilities and research services (all related to ongoing nutrition research); education programs for medical students, house staff, practicing physicians, and paramedical personnel; nutritional support services; and public information activities. The specific objectives of the CNRU program are:

- To create or strengthen foci in biomedical research institutions for multidisciplinary research in clinical nutrition in order to develop new knowledge about specific nutrients in health, human development, and the prevention and treatment of disease;

- To strengthen training environments and improve medical education; and

- To enhance patient care and promote good health by emphasizing clinical nutrition and generating nutritional information for the public.

Currently there are seven CNRUs in operation, five of which are funded by NIADDK. The following are examples of ongoing activities at these institutions:

- Studies to evaluate the efficacy of home tube feedings in support of patients with cystic fibrosis and patients with radiation colitis.

- A pilot project to identify malnutrition among hospital patients at the time of admission.

- Biweekly nutrition seminars for area nutrition/medical clinicians and basic scientists.
- A formal nutritional support service for infants and children, consisting of a nutritionist, a parenteral nutrition team, and a food technician.
- Preparation of booklets providing nutritional information for cancer patients.
- A study of trace metal requirements in patients receiving long-term parenteral nutrition.
- Laboratory investigations into the relationship of nutrition to autoimmunity and aging.
- A lecture series on controversial points of view in nutrition, including such subjects as vitamin "megadose" therapy and nutrition for mental disease.
- A pilot clinical study of protein nutrition and metabolism in pregnancy.
- Publication of an education series on nutrition, including controversies in clinical nutrition, nutrition and gastrointestinal disease, nutrition and surgery, nutrition and hematology, obesity, and drug-induced nutritional deficiencies in relation to aging.

KIDNEY, UROLOGIC, AND BLOOD DISEASES

RENAL PHYSIOLOGY/PATHOPHYSIOLOGY

Under the renal physiology/pathophysiology program, studies are supported not only on the normal structure and function of the kidney, including mechanisms of transport and fluid electrolyte dynamics, but also in the area of pathogenesis of renal diseases, such as glomerulonephritis, interstitial nephritis, acute renal failure, and numerous other disease processes. In past years, such research has increased the level of knowledge of renal metabolism and the immunological causes of renal disease and has resulted in the development of lifesaving measures such as kidney transplantation and dialysis with artificial kidneys, as well as advanced use of drugs, surgery, and supportive techniques that contribute to a better quality of life in many patients with these diseases.

The kidneys are vital organs that play a critical role in the maintenance of the body's internal environment. The kidney is the organ that regulates the composition, volume, and pressure of the body fluids. Another important function is the excretion of nitrogenous wastes and other end products of the body's metabolism.

In addition to maintaining the essential balance of water and electrolytes in the body, the kidneys also have hormonal functions including regulation of blood pressure through the renin-angiotensin system, stimulation of red blood cell production by erythropoietin, and regulation of vitamin D and mineral metabolism. When a disease process decreases the number of functioning kidney units (nephrons) below a critical point, the result is the appearance of uremia.

Highlights of Recent Advances

Some of the more recent advances in renal physiology and pathophysiology are highlighted below

- Cleansing of patient's blood plasma, by a technique known as plasmapheresis, in combination with immunosuppressive drug therapy is proving to be effective in halting the progression of Goodpasture's syndrome, a rare but often fatal condition involving the lungs and kidneys.
- An investigative method, isolated glomerular perfusion, is helping scientists to determine the effects of certain drugs on individual parts of the kidney, as well as aiding in the study of the immunologic basis of renal disease.
- A technique for measuring the metabolic activity of individual segments of a single nephron has been developed

Pathways of Research Progress

Immunopathogenesis of renal disease. Accumulated evidence indicates that immunological mechanisms may be responsible for a variety of renal diseases, including some forms of glomerulonephritis, nephrotic syndromes, and vascular diseases of the kidney. Extensive clinical, morphological, and serological studies in this area have been under way for several years and have considerably increased our knowledge of renal disease. These studies in both animals and humans have focused on models of human immune complex nephritis, studies of the complement system (a complex series of proteins that combine with antigen-antibody complexes) and complement deficiency, and characterization of nephritic "factors." Scientists are working on the characterization of one such factor, the C_3 nephritic factor (C_3Nef), which may be an autoantibody, a normally present antibody that, for reasons not yet known, begins to attack normal body cells in normal subjects and in certain disease states.

Researchers are also investigating autologous immune complex (AIC) nephritis in rats, which closely resembles human glomerulonephritis. This system has permitted researchers to study the ultrastructure of diseased glomerular capillaries, altered glomerular permeability, and early phases of both active and passive AIC nephritis.

Goodpasture's syndrome. Goodpasture's syndrome is a rare, rapidly progressive, and often fatal condition. Patients with Goodpasture's syndrome characteristically have simultaneous injurious deposition of either immune complexes or antibodies along the basement membranes of both the glomeruli and the pulmonary alveoli, resulting in bleeding from the lungs' alveoli (air sacs) and in glomerulonephritis, an inflammatory disease of the glomeruli, the blood-filtering units of the kidney.

It has been shown that plasmapheresis (a therapeutic procedure in which the patient's plasma is separated from blood, and the packed red blood cells are reinfused) significantly improved renal function in a short-term followup of many patients with Goodpasture's syndrome. Plasmapheresis combined with immunosuppressive drug therapy can reverse the progressive increase in kidney lesions; ordinarily, 88 percent of patients treated without plasmapheresis either die or require maintenance hemodialysis for survival. It has been suggested that plasmapheresis lowers total antibody protein levels, while the simultaneous immunosuppressive chemotherapy suppresses antibody formation by lymphocytes.

Functional profile of the isolated uremic nephron. Recent studies using a single isolated uremic nephron and a recently developed vibrating reed electrometer and ionization chamber for the measurement of minute quantities of radioactivity have shown that metabolic activity of individual segments of a single nephron can be instantaneously and continuously measured. Researchers utilizing this system have observed distinct metabolic differences between various segments of the nephron and have shown a significant pentose phosphate pathway in the collecting ducts in the cortex (outer portion) of the kidney.

Kidney prostaglandin synthesis in tissue culture. The kidney is an important source for the production of prostaglandins, fatty acid derivatives with a variety of hormone-like actions. The role of renal prostaglandins in modulating renal function in normal and in diseased states, however, is not delineated. A group of researchers is studying prostaglandin production in glomerular cells grown in tissue culture. A particular cell type that appears after about 2 to 3 weeks in culture resembles mesangial cells (cells from the membrane that supports the glomerulus) in its growth characteristics and its light- and electron-microscopic appearance. Through use of the prostaglandin precursor ^{14}C arachidonic acid in the medium containing these cells, it has been found that the cells incorporate arachidonic acid and metabolize it to produce prostaglandins. This ability of isolated cells to utilize ^{14}C arachidonic acid to produce prostaglandins was inhibited by the drugs indomethacin and meclofenemate, classic inhibitors of prostaglandin synthesis in other tissues. By isolating prostaglandin production in a specific segment of the nephron, scientists can begin to investigate the role of prostaglandins in the regulation of kidney function in health and disease.

Metabolism of polypeptide hormones. The clinical course of end-stage renal disease in patients maintained on dialysis is frequently complicated by a decrease or cessation in the secretion of erythropoietin (the renal hormone that stimulates production of red blood cells); abnormalities in the balance of polypeptide hormones, such as the pancreatic hormones insulin and glucagon, and the pituitary hormones prolactin and luteinizing hormone; and the metabolism of vitamin D.

Recent studies of normal humans and animals have established the importance of the kidney in metabolizing polypeptide hormones of varying molecular size. This function can be measured in terms of "renal clearance," which is the product of the rate of blood flow through the kidney and the amount of hormone the kidney extracts from the circulation. In studies of rat kidneys, it was found that large amounts of the medium-sized hormone insulin, its precursor proinsulin, and glucagon are extracted from the renal circulation and metabolized and broken down by renal tissue. These findings indicate that the normal kidney contributes substantially to the normal metabolic clearance of polypeptide hormones. When the kidneys fail, the levels of polypeptide hormones in the blood rise, partly in proportion to the relative amount of damaged renal tissues, and contribute to the pervasive metabolic abnormalities characterizing uremia.

Developmental renal physiology. Major maturational changes in renal physiology take place during the first months of life. Although these changes are even more important in the premature infant, the influence of prenatal and postnatal metabolic and environmental factors on the development and maturation of membranes, ion transport, metabolism, and acid-base balance and their roles in disease have not been extensively explored. In an effort to gain more knowledge on developmental renal physiology, researchers are currently attempting to characterize the passive movement of fluid and dissolved salts across the membranes of proximal tubules in the developing kidney; their ultimate goal is to determine whether the permeability of the membrane changes during development. Accumulated physiological data indicate that the response of developing tubules to ouabain, a sodium transport inhibitor, is similar to that of the adult tubule; the degree of swelling is also similar. Such studies are providing some clarification of the changes that take place in fluid transport across the renal tubule cells during kidney development—information that will be particularly useful in the management of kidney failure in premature infants.

Renin and hemodynamics. Potassium depletion is known to cause dramatic changes in blood flow dynamics and in plasma renin activity, an essential component in the complex system of blood pressure regulation. Studies of the relative roles of potassium, angiotensin (a blood pressure regulating hormone), and prostaglandins in controlling hemodynamics during dietary potassium deficiency are under way, as are studies of the mechanism of hyperreninemia observed during chronic potassium deficiency. Results to date indicate that after 14 days of dietary potassium deficiency, marked changes in both systemic and renal hemodynamics occur. According to investigators, the observed increase in renin levels is associated with a decrease in fluid delivery to the distal nephron and an increase in renal baroreceptor (blood pressure receptor) tone. Consequently, renin release could be caused by stimulation

of either the macula densa or the baroreceptors, or by a direct effect of potassium deficiency. Investigators have been able to demonstrate that this effect is not a result of acute hypokalemia (potassium deficiency), since perfusing normal kidneys with hypokalemic solution did not increase renin levels. The results of this research help to explain further the role of the kidney in the regulation of blood pressure.

Isolated glomerular perfusion—a new investigative tool. Institute grantees have developed a technique, isolated glomerular perfusion, by which glomerular dynamics in the isolated dog glomerulus can be measured **in vitro**. With this technique investigators will be able to determine the effect of various pharmacologic agents on glomerular function and to measure directly the glomerular ultrafiltration coefficient in normal and abnormal conditions. Further, it will be possible, for the first time, to compare differences in glomerular dynamics between glomeruli located in the outer zones and those located in the inner zones of the kidney.

Although the technique was developed to aid understanding of the physiologic control of glomerular filtration, its most important application may be as a powerful tool to study the mechanisms of development of immunologic renal disease. For example, it is known that many renal diseases occur as a consequence of the deposition of immune complexes within the glomerulus (clogging its filtering ability) but the mechanisms involved in the deposition of these immunogenic substances are not known. Using isolated glomerular perfusion, investigators will seek to determine the characteristics of specific immune complexes (i.e., size, shape, or charge) that may lead to their deposition within the glomerulus and what pharmacologic agents (e.g., steroids, histamine) may modify these characteristics. It is anticipated that, with these data, the pathophysiologic basis of specific renal diseases can be better understood.

CHRONIC RENAL DISEASE

Failure of the kidney to maintain the volume and composition of body fluid and a chemically balanced internal milieu leads to a panorama of problems culminating eventually in the condition known as uremia once renal failure is sufficiently advanced. Uremia affects more than 10 per 100,000 persons annually. The progression of many chronic renal diseases is not significantly affected by therapeutic interventions, and management is often symptomatic and supportive. Dialysis and transplantation provide prolonged survival of these patients but these treatments are less than ideal.

The adaptive responses of the kidney to loss of functioning tissue have been studied extensively. Much is known about the maintenance of salt and water homeostasis, acid-base balance, and calcium metabolism. Our understanding of the factors that cause irreversibility, development of sclerosis of small vessels and of the glomerular mesangium, and the development of interstitial inflammation and fibrosis in response to glomerular or tubular injury—common to the progression of most chronic renal disease—is inadequate. The pathogenesis of **acute** renal failure (in contrast to gradual progressive chronic renal insufficiency) is not fully understood; the factors contributing to its persistence and to the onset and course of recovery are important unresolved problems, and mortality from acute renal failure is still close to 50 percent.

Our limited understanding of the increased susceptibility to infection and the pathogenesis of accelerated atherosclerosis in uremic patients (the two most frequent causes of death) causes important pragmatic problems. The pathogenesis of such uremic symptoms as nervous system abnormalities, bone disorders, membrane dysfunction, growth retardation in children, and anemia remains poorly understood. Transplantation has limited success, in part because the determinants of rejection of transplanted tissue and its mechanisms are not understood completely.

Through NIADDK-supported investigations at the basic, applied, and clinical research levels, technological developments such as kidney transplantation and maintenance dialysis with artificial kidneys are now being applied extensively in actual practice.

These advances make useful lives possible for many patients who otherwise would have died of uremia after loss of kidney function due to acute or chronic

Highlights of Recent Advances

The following highlight some of the recent therapeutic advances in the treatment of chronic renal disease. Clearly, NIADDK's continuing emphasis on basic research in chronic renal disease is essential to fill in the gaps in present knowledge and to translate that knowledge into improved care.

- Transplanted cadaver kidneys remain functional considerably longer if the graft recipient has been given several blood transfusions prior to transplantation, during the earlier stage of maintenance dialysis.
- Continuous ambulatory peritoneal dialysis—developed under NIADDK sponsorship—is a novel approach to self-treatment of chronic renal disease that provides added convenience to the patients and, in most cases, does not require dietary restrictions (in contrast to hemodialysis)
- Caloric supplementation has been found to be essential to maintain normal growth and weight gain for children with uremia who are on maintenance dialysis.
- It has been found that zinc deficiency in dialysis patients, which causes diminished taste acuity and appetite, can be corrected by long-term daily supplementation with oral zinc.

renal disease. Hemodialysis (use of an artificial kidney machine to wash out poisonous wastes directly from the blood) has been improved through new techniques; peritoneal dialysis (a procedure of instilling a special dialysate fluid into the abdominal cavity for toxic waste clearance across the peritoneal membrane) has become a clinically effective alternative to hemodialysis in the treatment of end-stage kidney disease; and kidney transplantation has evolved from a method of last resort to the treatment of choice for many patients with irreversible renal failure.

Pathways of Research Progress

Kidney transplantation. Because of the limited supply of donor kidneys from compatible, closely related, living donors, the majority of transplant patients with end-stage renal disease receive cadaver kidney grafts. The overall rate of functional cadaver graft survival remains substantially below that for transplants from closely related, living donors, where a 5- to 8-year graft survival can be expected in about 60 to 70 percent of cases. In an effort to improve graft survival, scientists have studied the effect of various factors, including pretransplant blood transfusions, on graft survival.

Analysis of graft survival data shows that success of cadaver kidney transplants increases considerably in proportion to the number of blood transfusions (up to 20) that the patient has received prior to transplantation during the period of maintenance dialysis. On the basis of these and similar studies, it is now suggested that candidates for eventual cadaver kidney transplants be transfused during the period of maintenance dialysis preceding transplantation.

Antilymphoblast globulin (ALG) in renal transplantation. Of critical importance in renal transplantation is control of the recipient's immune response so that the transplanted kidney is not destroyed. A cooperative prospective double-blind study is being conducted to evaluate the efficacy of ALG as an immunosuppressive adjunct in cadaver renal transplant patients. Patients are randomized to receive either human serum albumin (placebo) or equine ALG, and are stratified by age, histocompatibility match, and transfusion status. The immunosuppressive drugs azathioprine and prednisone are administered to all patients in the study.

Preliminary results of the trial showed that for approximately half of the patients with a history of blood transfusions, graft function in the ALG group was 75 percent at the end of the first year, compared to 58 percent in the placebo group. Patient survival was 86 percent in the ALG group, 81 percent in the placebo group.

In the final analysis, the relative beneficial contributions of each factor will be analyzed to help formulate the best therapeutic approach for renal transplants.

Renal transplant rejection. Approximately 25 percent of living, related donor grafts and 45 percent of cadaver donor grafts are lost from irreversible rejection during the first year after transplantation. Histocompatibility testing is conducted by means of studies of lymphocytes of both the potential recipient and the donor. An antigen system found on the vascular endothelial cells, but not on lymphocyte or renal cells, exhibits a high correlation with the clinical course of patients undergoing a renal transplant. Essentially all patients who had antivascular endothelial cell antibody before transplantation, or developed it afterward, lost their grafts due to rejection. The investigators have shown that this antigen system (vascular endothelial cell) is different from the conventionally used HLA-A tissue typing system and from other systems as well, but may well be of superior predictive value.

The findings of this study are a significant step toward the important goal of being able to predict immunologic graft rejection and thus to improve kidney transplantation as a successful treatment modality for the chronic renal failure patient.

Nutritional status of children with chronic renal insufficiency. Nutritional deficiencies in uremic children have been linked to impaired growth and diminished muscle mass. However, there are no standards for the assessment of nutritional status in children with chronic renal insufficiency.

In a recent study, researchers determined the biochemical indices of body protein mass, anthropometric measurements, and caloric intake over a 3-year period of 20 uremic children. Each child received caloric supplementation of the regular diet during 1 year of the study. With caloric supplementation, the energy intake increased from 77 to 99 percent of recommended dietary allowance and growth rates increased from 70 to 96 percent of values expected for the patient's age. In the third year of the study, when children were allowed to choose their own diet, caloric intake decreased to control levels and anthropometric indices regressed.

It was concluded that anthropometric measurements are a reliable and reproducible indicator of moderate energy deprivation in children and that deliberate and monitored caloric supplementation is essential to maintain normal growth and weight gain in uremic children on maintenance dialysis.

Dialysis therapy. Continuous purification of the blood of uremic patients undergoing peritoneal dialysis or the new extracorporeal hemofiltration process requires large quantities of expensive solutions free of bacteria and their fever-producing contaminating products (pyrogens). In an effort to reduce the cost of such solutions, scientists have tested hollow-fiber ultrafilters made of highly porous artificial membranes for the removal of bacteria and pyrogens from typical dialysis fluid. Results have been successful; patients now can receive infusions of solutions sterilized and purified by ultrafiltration during routine maintenance hemofiltration treatment for uremia. This low-pressure filtration process may be accomplished in one step and is adaptable to solutions containing pretreated municipal tap water. If quality control can be maintained, the clinical application of these solutions could significantly reduce the cost of therapy.

Zinc supplementation. An association has been found between zinc deficiency in dialysis patients and diminished taste acuity, resulting in poor appetite. Results suggest that long-term daily supplementation of the diet with oral zinc is likely to increase serum and red blood cell zinc levels, restore taste acuity, and improve appetite in zinc-deficient dialysis patients. Since renal impairment is associated with excessive excretion of the blood protein albumin, and nearly 65 percent of serum zinc is bound to albumin in the blood, prolonged urinary loss of this protein during chronic renal failure prior to dialysis in the face of marginal daily zinc intake may be the factor largely responsible for zinc deficiency in such patients.

Serum lipid abnormalities. Elevated serum triglyceride (neutral fat) levels are a significant risk factor for atherosclerosis and a frequent complication of hemodialysis in uremic patients. The use of clofibrate, a drug with the capacity to restore serum cholesterol levels to normal, has been contraindicated in patients with renal failure because it causes muscle damage when given at the usual recommended dosage. However, results of an NIADDK-supported study demonstrate that low-dose clofibrate therapy effectively reduces elevated serum triglycerides and increases the beneficial high density lipoprotein cholesterol levels toward normal, thereby diminishing the risk of atherosclerosis and subsequent coronary artery disease in uremic patients on maintenance hemodialysis.

Continuous ambulatory peritoneal dialysis. In the technique known as intermittent peritoneal dialysis, the lining of the abdominal cavity (the peritoneum) is used as the membrane through which uremic waste products are filtered and removed from the patient. Blood is not circulated and purified outside the body as in hemodialysis. Instead, a sterile wash solution is repeatedly introduced into the abdominal cavity and withdrawn from it through a small tube permanently implanted in the abdomen. Each time, the wash solution remains in the abdomen about 20 minutes or longer while toxic uremic substances are moved from the blood through the peritoneal membrane into the flushing fluid by osmosis. This procedure is repeated a number of times during each treatment session. One of the major drawbacks of the technique is that treatment time may be twice as long as with hemodialysis.

A potentially marked improvement in peritoneal dialysis is currently under investigation, however. Institute-supported researchers are studying the technique of continuous ambulatory peritoneal dialysis (CAPD) to define ways to individualize treatment according to a patient's needs and to determine the procedure's long-term effects. At present, CAPD, which was developed with NIADDK sponsorship and organization, appears to be a simple and potentially inexpensive form of therapy that allows the patient greater freedom than does hemodialysis and, in many cases, fewer dietary restrictions.

The increasing acceptance of CAPD by patients and physicians, along with its potential economy, makes it a promising new approach to maintenance treatment of end-stage renal disease.

Uremic pericardial effusion. Pericardial effusion, the accumulation of fluid in the sac enveloping the heart, is a complication of dialysis therapy and is considered intractable when it does not respond to conservative management of uremia, improved dialysis regimens, or systemic therapy with anti-inflammatory drugs. As an alternative to surgical stripping of the sac-like pericardium, local instillation of a nonabsorbable steroid through an indwelling pericardial drainage catheter has been attempted. This procedure, which has been used in a limited number of patients, has reduced morbidity, mortality, and length of hospital stay of uremic patients with intractable pericardial effusion. The preliminary results point to combined percutaneous catheter drainage and local nonabsorbable steroid instillation as a technique superior to surgery in the management of complicating pericardial effusion in uremic patients.

Dialysis osteodystrophy. The term "renal osteodystrophy" refers to the bone demineralization that is observed in 10 to 25 percent of patients with end-stage renal disease and embraces derangements in calcium and magnesium ion metabolism, soft tissue calcification, alteration in parathyroid hormone and vitamin D metabolism, defects in calcium absorption, and the skeletal fragility and bone pain that attend the clinical course of uremic patients on dialysis therapy.

Recent research by NIADDK grantees has shown that treatment with 1,25 dihydroxyvitamin D_3 (usually produced by the normal kidney but missing in kidney failure) is effective in reversing many manifestations of the marked secondary hyperparathyroidism commonly present in patients with advanced renal failure and/or undergoing hemodialysis. Observations show that elevated plasma levels of parathyroid hormone were reduced to normal in uremic patients treated with this active metabolite of vitamin D and might be effective in preventing the development of overt secondary hyperparathyroidism.

UROLOGIC DISEASES

The functions of the kidney and lower urinary tract must be considered together. When the system is functioning properly, the urine produced by the kidneys flows freely through the ureters to the bladder, where it is stored until it is excreted. Obstruction to this normal flow by conditions such as enlargement of the prostate gland, kidney stones, neuromuscular disorders of the bladder, or congenital abnormalities, causes stasis (slowing of flow), which leads to malfunction of the kidneys and may provide an opportunity for infection to occur.

Urinary tract infection, neuromuscular disorders of bladder function, obstruction, and kidney stone disease account for about 20 percent of deaths from kidney disease. Together these interrelated conditions account for a major portion of all disability caused by disorders of

the urinary tract, and they affect over 12 million people in the United States each year.

Limited knowledge of the normal function of the urinary system restricts our insight into the causes and development of the multiple diseases that affect this system. For this reason, NIADDK supports many basic science investigations in both normal and abnormal lower urinary tract physiology as well as clinical studies of techniques to control resulting disorders.

In the field of urology, new drugs such as antibiotics and others that permit effective treatment of serious infections have been developed, and advances in urologic surgery have led to the ability to repair congenital anomalies and surgically reconstruct diseased organs. Specialized Centers of Research (SCORs) for urolithiasis have been established, with the goal of increasing research efforts from a variety of disciplines, to clarify further the underlying physiologic mechanisms and metabolic interactions and to delineate new treatment modalities to prevent or control urolithiasis.

Highlights of Recent Advances

The following highlight some of the recent advances and ongoing research in the field of urology

- New surgical techniques have been developed which permit restoration of damaged or congenitally absent ureters and which successfully establish valve action to prevent urine reflux.
- An epidemiologic study to identify risk factors in the development of urinary tract stone is under way.
- NIADDK grantees are studying new methods for measuring oxalate (a frequent constituent of kidney stones) in biological fluids.
- Guidelines for the treatment of bacterial prostatitis with antibiotics and other drugs are being developed through study of the effects of various pharmacological agents on animal tissues.
- Progress has been made in the development of an electrical pacemaking prosthesis to aid patients who have dysfunction of the bladder.

Pathways of Research Progress

Nephrolithiasis and urolithiasis. More than a million people are hospitalized in the United States each year for the treatment of kidney and urinary tract stones. A number of years ago, only about 5 percent of these patients had a known underlying cause for stone formation, but research in progress may permit identification of specific causes for renal stones in almost 85 percent of the remaining patients.

Ongoing research suggests that abnormal handling of calcium by either the small intestine or the kidney may be responsible for urinary excretion of excess calcium and kidney stone formation. Investigators have found that excess urinary calcium predisposes the individual to kidney stone formation. Excessive levels of calcium in the blood may be due to enhancement of calcium transport from the intestinal lumen to blood vessels in the jejunum, and this process may be mediated by high levels of a vitamin D metabolite.

Excessive uric acid formation in the body, or a purine-rich diet, promotes kidney stone formation by increasing renal excretion of uric acid (a metabolic breakdown product of purines) and supersaturating urine with sodium urate, thus favoring crystallization of insoluble calcium urate salts, directly or indirectly. Investigators have found that allopurinol therapy (also used in treating gout to prevent excessive synthesis of uric acid in the body) decreases urinary uric acid and saturation with monosodium urate, thus inhibiting calcium-containing stone formation and ultimately yielding significant clinical benefits.

From this work, researchers have developed a protocol for evaluation and diagnosis of different causes of calcium urolithiasis. From data retrieved and analyzed by computer, scientists will be able to formulate the minimal diagnostic criteria for different causes of urolithiasis, to assess important physiological interrelationships, and to define the clinical presentation for each disorder. As a complement to this work, an epidemiologic study is being conducted to identify a population of persons with hypercalciuria (excess calcium in the urine). From data collected in this study, researchers hope to identify possible risk factors for the development of stones, including obesity, occupation, use of medications, and urinary tract infections.

NIADDK grantees have also established that the state of the urothelium (cellular lining of the lower urinary tract) profoundly influences the characteristics of the stone-forming process. For example, if urothelial injuries are induced, calcium oxalate crystals are more likely to be nucleated at the site of injury, and the minute crystals formed are more likely to adhere to the damaged urothelium than to a healthy epithelial lining. These phenomena are believed to be important in the initiation and progression of human stone disease. These experiments suggest that the nature of the interface between the urine and the bladder wall, a factor neglected in most crystallization studies related to biological systems, may be more important than previously realized.

Although many urinary stones are high in oxalate content, few patients with stones have a significant increase in urinary oxalate excretion. A major deficiency in the study of oxalate metabolism is the lack of a simple, reliable method of measuring oxalate in biological fluids that can be adapted to microanalysis by renal physiologists. Institute-supported research groups at present are studying the problem and working on the development of such techniques.

Renal colic pain from ureteral calculi (stones lodged in the ureter) is one of the most common medical/surgical emergencies, causing considerable suffering and sometimes permanent damage to the kidney or ureter. Researchers are studying the effects of various urine

flow rates on ureteral activity and the effects of numerous agents such as glucagon on activity of the normal ureter at various flow rates. These experiments are an attempt to determine which factors improve or hinder the progress of kidney stones down the ureter.

Effective therapy and the prevention of recurrent urolithiasis have most commonly been directed toward favorably altering the state of saturation of crystals that may promote stone formation, although knowledge of the factors affecting crystal dissolution is limited. Current Institute-sponsored research is aimed at developing techniques for evaluating and altering a patient's potential for stone formation to provide effective preventive therapy.

Congenital anomalies of the urinary tract. Pediatric urology concerns itself with the diseases of the urinary transport system in children and of the reproductive tract in boys. Like primary renal disease in infants and children, abnormalities of urinary drainage are eventually reflected by a host of adverse effects upon the growing child. Urinary stasis, a very common concomitant of partial obstruction of the urinary tract at any level, predisposes to urinary infection, which in turn produces accelerated, and often permanent, kidney damage.

Developmental anomalies give rise to a variety of urologic diseases, and increasing knowledge of these diseases has prompted the search for more advanced diagnostic and treatment technologies. NIADDK-supported scientists have pioneered the use of sophisticated diagnostic procedures, such as X-ray motion pictures of the urinary tract and cinefluorography of the bladder, in measuring and interpreting pressure and flow changes in the lower urinary system as a result of congenital anomalies. Advanced surgical corrective procedures have also been developed with Institute support. One group of investigators has devised an effective technique for reimplanting malfunctioning ureters in the bladder to reestablish normal valve-like action to prevent the potentially dangerous reflux of bladder urine up the ureters into the kidneys. In addition, other researchers have developed surgical procedures to restore damaged or congenitally absent ureters.

Bladder dysfunction. A specialized area in the field of bladder physiology is the study of the nervous regulation of bladder filling and emptying. Neuromuscular malfunction of the bladder is a common problem. Disturbances in control of urination are seen in some diabetic patients, many mentally retarded persons, patients with strokes, and patients with spinal cord injury.

Following damage to local nerves or to the spinal cord, management of bladder emptying and defense against bladder infection (caused by urinary residues in a poorly functioning bladder) are two of the most difficult problems facing paraplegic patients. To combat these problems, investigators are experimenting with an electrical pacemaking prosthesis that can induce periodic bladder emptying and thereby decrease the chances of recurrent urinary tract infection. This technique involves implantation of electrodes in the muscle of the bladder wall. Power delivered to the electrodes from an external radio frequency transmitter stimulates the bladder musculature.

Vesicoureteral reflux. Because the management of children with vesicoureteral reflux of urine (abnormal upward motion of urine from the bladder toward the kidney) remains controversial, a multicenter prospective study was recently funded by NIADDK to define optimal treatment for this problem. A proportion of the children with vesicoureteral reflux show retardation of renal growth, progressive renal scarring and, in a few cases, loss of renal function. However, it is unclear whether reflux alone, or reflux in combination with infection or obstruction, is responsible for these changes, and whether surgical correction of the reflux can prevent or arrest any of these changes. This prospective, randomized study—involving the collaboration of 15 institutions that offer care for pediatric patients—will determine whether young children with vesicoureteral reflux are best treated by prophylactic antibiotic therapy or by surgical correction through ureteral reimplantation. Medical treatment will include antibacterial therapy with small doses of drugs for as long as the reflux persists and for 6 months thereafter. Followup studies will be at 6 months, 2 years, 3-1/2 years, and 5 years in the medically treated group. The results of this study will be transplanted into improved care for children with vesicoureteral reflux, prevention of its adverse effects, and improved quality of life.

Urinary tract infection. Urinary tract infections are among the most common bacterial diseases in clinical practice, occurring in 25 percent of all women at some time in life and ranging in severity from simple growth of bacteria in the urine without symptoms to severe kidney infection and failure of kidney function. Although the bacteria responsible for most kidney infections have been identified as those normally present in the bowel, the factors responsible for their ability to invade and damage the urinary tract and kidney have not been identified. Scientists studying the mechanisms of the urinary bladder's natural resistance to retrograde infections by bacteria from the rectum hope to identify some of the causes of bacterial colonization of the urinary tract. Current research indicates that there is a normally occurring mucopolysaccharide that prevents adherence of the bacteria to ureters and the bladder wall and allows them to be washed out by the urine flow even if they inadvertently gain entrance to the lower urinary tract. Investigators suspect that this mucopolysaccharide is the first line of defense of the bladder to bacterial invasion. Further study should provide insight into the causes of recurrent urinary tract infection, the factors modulating the individual's immunologic defense systems against infection, and how they may be strengthened to prevent recurrent cystitis.

Bacterial prostatitis. Guidelines for treatment of bacterial prostatitis with chemotherapeutic agents and antibiotics are being developed by NIADDK-supported

scientists studying the pharmacological effects of different agents. Results indicate that acidic substances such as ampicillin, cephalosporins, cinoxacin, and sulfamethoxadole are concentrated in interstitial prostatic fluid in amounts within the therapeutic range of treatment for most gram-negative bacterial infections. This suggests that the efficacy of acidic substances in the treatment of prostatitis may have been underestimated in the past and that therapeutic acidic drug levels in prostatic fluid may offer an effective approach to treatment.

In related studies examining concentrations of chemotherapeutic agents and antibiotics in the vaginal mucosa and urethra of dogs, investigators report that acidic and basic substances concentrate in the vaginal mucosa in a manner similar to that in the prostate. This research could lead to clinical innovations in the treatment of recurrent urinary tract infections in women.

Program Accomplishments—Specialized Centers of Research in Urolithiasis

SCORs are used by NIH to fund multidisciplinary investigations in specific diseases or biomedical problems. Urinary tract stone disease is one of the most common renal-urologic diseases and represents a significant world health problem. In the United States, at least 1 percent of the population will develop urinary tract stones, primarily in the kidneys. The condition, while not usually fatal, causes considerable suffering, morbidity, and loss of work. Prior to the initiation of the urolithiasis SCORs, support for research into the causes and treatment of urolithiasis was relatively low. Five SCORs in urolithiasis were awarded for the first time in 1977 on the recommendation of the NIADDK Advisory Council and Congress. The SCORs were established to meet the need for a planned and coordinated program of basic and clinical research specifically directed at improving the diagnosis, treatment, and prevention of urolithiasis.

Each SCOR is an identifiable organizational unit within an academic institution and has the central theme of urolithiasis research. The SCOR pools resources from multiple disciplines and departments in both basic and clinical sciences, allowing those with in-depth knowledge and common research interests to work together toward specific objectives. Within this framework, the divergent resources, facilities, and expertise in the many disciplines involved can be utilized to meet scientific goals that would be difficult to accomplish by traditional investigator-initiated grant awards.

BLOOD DISEASES

The hematology program of NIADDK supports investigations into basic aspects of normal and abnormal blood cell components and function and pathogenesis, diagnosis, and treatment of diseases of the blood. It covers a spectrum that ranges from determination of the molecular structure of abnormal types of hemoglobin (the protein that enables blood cells to act as oxygen carriers) to clinical application and evaluation of new treatment methods of certain blood diseases. This research increases both fundamental and applied knowledge about blood and has led to improved management of many specific diseases.

Hematologic investigations supported by NIADDK encompass five major disease categories: anemias of genetic origin, nutritional anemias, metabolic disorders, disorders of blood cell production, and autoimmune hematologic disease. Advances brought about by NIADDK-supported research on blood clotting factors and hemoglobinopathies during the last three decades have not only improved our ability to diagnose and treat hemophilia and sickle cell diseases, but these advances have also benefited basic investigations in other NIADDK programs and research programs in other NIH Institutes.

Highlights of Recent Advances

Significant advances in understanding normal blood cell function and disease pathogenesis, ranging from development of treatment modalities to clinical application and evaluation of treatment of relevant diseases, have occurred in recent years The following highlights some of these recent advances.

- A safe and highly sensitive method has been developed for prenatal diagnosis of sickle cell disease and Cooley's anemia.
- Abnormal red blood cell adherence to vascular epithelium points to a specific membrane defect in sickled cells, a finding that may lead to new therapies for sickle cell disease
- A derivative of chloramphenicol (CAP), an antibiotic, has been identified as a factor in bone marrow toxicity leading to aplastic anemia following CAP exposure.
- The cause of neonatal thrombocytopenic purpura (decreased platelet count) has been shown to be quite similar to that of Rh incompatibility in newborns.

Pathways of Research Progress

Neonatal thrombocytopenic purpura. Recent investigations have pinpointed the cause of neonatal thrombocytopenic purpura, a serious blood disease that occurs in newborn infants. Blood platelets (or thrombocytes) are cell-like structures that circulate in blood and aid in the normal clotting process. Following the finding that blood platelets contain a specific pattern of inherited antigens, NIADDK-supported scientists have shown that antibodies formed against platelet antigens can cause diseases and clinical complications that are similar in many respects to disorders caused by antibodies against the known red blood cell antigens. The researchers found that at least seven different "types" of human platelets exist, the differences being similar to the differences in types of red blood cells that are responsible for the well-known blood groups, A, B, and O.

Using a method developed to detect platelet antigens, research workers have shown that most cases of platelet deficiency and bleeding in newborn infants (neonatal thrombocytopenic purpura) are due to a defensive antiplatelet antibody formed by the mother against an antigen in the baby's platelets that is inherited from the father and is "foreign" to the mother. In the families studied, the mother's antibody was transmitted into the fetal circulation through the placenta and caused bleeding in the infant by destroying the infant's platelets. Thus, the etiology of this disease was shown to be quite similar to that of the serious blood cell destruction in infants caused by mother-fetus incompatibility of the well-known red cell Rh factor antigens.

Porphyria. The term "porphyria" embraces a group of diseases characterized by the appearance in the urine of a variety of abnormal forms of porphyrin (breakdown products of the red blood cell pigment, hemoglobin). Symptoms of these diseases involve the skin, abdominal organs, and, at times, the nervous system; in severe cases, the disease may be fatal.

A new enzyme-free intermediate in the porphyrin biosynthetic pathway, preuroporphyrinogen, has been discovered and has been shown to be the long-sought substrate for the enzyme cosynthetase in forming uroporphyrinogen III, the precursor of heme (the iron-containing blood pigment). This substrate is the key to a previously unsuspected developmental pathway. Its discovery has major significance for understanding the control of heme synthesis in vivo and will be of considerable use in designing physiologic therapies for porphyria.

Nutritional anemias. It has been recognized for many years that intestinal iron absorption is affected by the status of body iron stores and by the demands and rate of erythropoiesis (red blood cell formation in the bone marrow). An iron-deficient diet, blood loss, induction of hemolysis (blood cell destruction), and stimulation of erythropoiesis are factors that can affect iron absorption.

Similarly, it is known that iron-deficient animals absorb increased amounts of divalent metal ions, such as cobalt, lead, zinc, and manganese. Recent studies have shown that while an iron-deficient diet will produce a marked increase in the absorption of other divalent metals, stimuli that normally tend to enhance iron absorption have little or no effect on the absorption of other divalent metals. This suggests that an iron-deficient diet and factors such as experimental phlebotomy (bloodletting) have different effects on the pathway of iron absorption in the mucosal cell. Ultrastructural studies in combination with radioautography and benzidine staining of heme are being used to delineate the absorptive pathway of hemoglobin iron in an effort to clarify the relationship between control factors and to help develop therapeutic regimens.

Erythropoietin deficiencies and red blood cell production. A major problem in patients with chronic renal failure, even in those who are adequately dialyzed, is anemia. Research directed toward correcting this problem has demonstrated that replacement therapy with the hormone erythropoietin, which is normally produced by healthy kidneys, appears promising. Erythropoietin stimulates the production of red blood cells; without it, normal erythropoiesis cannot take place. In chronic renal failure there is little functioning kidney tissue left to produce sufficient erythropoietin, and marked retardation and diminution of red blood cell production ensues, resulting in anemia. While there are other factors underlying the anemia of chronic renal failure, such as shortened red blood cell life and toxic damage, erythropoietin deficiency is considered the most important single factor.

Exogenous erythropoietin is scarce; thus, effective treatment of the anemia associated with chronic uremia is not yet possible. One approach to the problem of erythropoietin production might be in harvesting the hormone from large cell culture systems. NIADDK-supported research has shown that fetal mouse liver cells grown under controlled environmental conditions provide a greatly increased surface area and high cell yield of erythropoietin. Erythropoietin production by fetal liver cells has been shown to be stimulated by the addition of physiologic doses of testosterone to the culture and by lowered oxygen in the culture environment. Adequate production of erythropoietin from cell culture and the use of exogenous erythropoietin replacement therapy in patients with chronic renal failure may, in the future, help to reduce the morbidity classically associated with this disorder.

Immunologic suppression of bone marrow. Studies directed toward understanding disorders of blood cell production have revealed evidence for immunologic, cell-mediated suppression of bone marrow growth in some patients with aplastic anemia (anemia characterized by cessation of red blood cell formation in the bone marrow). Marrow cultures from approximately 20 percent of aplastic anemia patients studied exhibited no erythroid colony formation until T-lymphocytes (lymphocytes stimulating antibody production) were removed. After removal, virtually normal colony formation was observed, suggesting that the clinical failure of bone marrow growth in these patients may be due to direct interaction between circulating lymphocytes and the erythroid colony-forming unit in the marrow. Increased knowledge of the cell-mediated, immunologic suppression of bone marrow in aplastic anemia may provide further insight and guidance for potential therapies for this insidious, often fatal, disorder.

Toxic suppression of blood cell production. The nitroso derivative of the antibiotic agent chloramphenicol has been found to be the likely cause of bone marrow toxicity leading to aplastic anemia in selected cases following exposure to CAP. The mechanism leading to aplastic anemia and leukemia from CAP is uncertain but has long been thought to be related to the presence of the nitrobenzene moiety in the antibiotic compound. The CAP analog thiamphenicol differs from CAP by substitution of the nitrobenzene group. Thiamphenicol

exhibits similar antibiotic efficacy but has not caused documented cases of aplastic anemia. Whereas CAP containing the nitrobenzene moiety inhibits DNA synthesis only in high concentrations, with reversibility, the nitroso form inhibits DNA synthesis at much lower concentrations irreversibly. Thus it is postulated that the nitroso derivative is formed from CAP in a predisposed host, leading to aplastic anemia or leukemia. This line of research may lead to a discovery of the precise biochemical mechanism of marrow toxicity of CAP and an understanding of one mechanism of marrow dysfunction.

Erythrocyte membrane composition. NIADDK-supported research has led to the collection and partial characterization of a homogeneous preparation of human erythrocyte membrane protein kinase. The phosphorylation-dephosphorylation of erythrocyte membrane proteins is thought to play an important role in transforming and deforming the shape of red blood cells, as is the case in hereditary spherocytosis and the diseases characterized by abnormal erythrocyte shapes. The identification of the enzyme responsible for the phosphorylation reaction represents a significant step toward understanding this important erythrocyte membrane phenomenon. It may also improve insight into some of the diseases associated with abnormally fragile erythrocytes such as the hemolytic anemias.

Cooley's anemia. Cooley's anemia is an inherited anemia characterized by synthesis of abnormal types of hemoglobin and formation of red blood cells with abnormally thin and fragile cell walls which have an abnormally brief lifespan. Clinically the disease is characterized by mongoloid features, fatigue, severe anemia, jaundice, cardiac and splenic enlargement, and death in the early adult years. Research efforts have been directed toward developing methods for prenatal diagnosis, and NIADDK grantees have reported the identification of specific hemoglobin gene sequences in cultures of cells aspirated prenatally from the amniotic fluid surrounding fetuses known to be at risk for Cooley's anemia. Previously, analysis of fetal blood cells, taken from a placental blood vessel **in utero**, to determine their ability to synthesize normal hemoglobin was the focus of research in this hereditary disease. The new method involving amniocentesis is considerably less hazardous and represents a great improvement in prenatal diagnosis methodology.

In related research, studies on the development of new iron chelating (iron binding) compounds for clinical use in conditions like Cooley's anemia are increasing. This aspect of research on Cooley's anemia is of utmost importance; the only treatment currently available to alleviate the severe anemia in this condition is repeated transfusion of normal blood. This treatment, however, eventually leads to life-threatening iron overload in vital organs of the recipient, particularly the kidneys, liver, and heart. This iron overload causes functional failure of various organs and may lead to death. An intensive search is under way to find a suitable, safe, and effective drug (preferably one that can be taken orally) to control the potentially fatal buildup of iron in critical tissues of affected patients.

Hemophilia. Health care for the patient with hemophilia changed dramatically in the mid-20th century as a result of two important research achievements: the separation of blood plasma into component parts (fractionation) in 1954, and the identification of Factor VIII, the factor missing from the blood of most hemophilia patients, in 1964. These discoveries prompted the development by NIADDK intramural scientists of the plasma clotting factor concentrates that have become a key component of therapy for hemophiliacs. Prevention of extensive bleeding in hemophilia, even in previously life-threatening dental extractions and major surgery, is now possible.

Additionally, Institute grantees have shown that potent concentrates of antihemophilic globulin (AHG) derived from animal sources can control life-threatening hemorrhages in patients with circulating antibodies to AHG. About one hemophilic patient in five acquires such antibodies and poses a difficult therapeutic problem because huge amounts of human plasma, the source of AHG, are required to control any bleeding. In an effort to solve this problem, scientists have been able to produce abundant quantities of antihemophilic factor by perfusing pig spleens with human hemophilic blood. This work suggests that splenic hemotransplantation may provide a permanent source of the large quantities of AHG needed for hemophilic patients.

As the use of cryoprecipitates and other blood concentrates to control bleeding has become widespread, the emphasis in management of a hemophilic patient has changed from solely preventing hemorrhage to providing comprehensive care.

Sickle cell anemia. Sickle cell anemia is an inherited disorder in which defective beta globin genes produce chemically and structurally abnormal hemoglobin molecules. These abnormal molecules are responsible for deforming or sickling red blood cells which, because of their deformed shape, may clog small capillaries. This blockage produces acute pain and results in the loss of functional tissue in affected organs. The disorder is found primarily among the black population of the United States, where from 8.0 to 13.0 percent of the population are heterozygous carriers of the trait (asymptomatic but capable of passing on the defect) and about 0.3 to 1.5 percent are homozygous, symptomatic patients. Couples consisting of heterozygous individuals carrying one defective and one normal beta globin gene each have a 25 percent chance of conceiving a child who will have sickle cell disease.

Understanding of sickle cell anemia has improved significantly in the past three decades, with research focusing on the molecular structure of normal and sickle cell hemoglobin, techniques for early diagnosis, and methods of treatment. With NIADDK support a simple, practical, and inexpensive procedure was developed for detecting the disease by means of dried blood specimens on filter paper, a method first used in mass screening of newborn infants for phenylketonuria.

The technique of aspirating fetal blood from the placenta for prenatal diagnosis of sickling, a technique that still carries some risk to the fetus, was introduced as well as a more recently developed, safer, technique using amniotic fluid to obtain fetal cells for analysis of DNA. Amniocentesis is regarded as a procedure that is relatively safe for both mother and fetus. This revolutionary method of DNA analysis for the prenatal diagnosis of sickle cell anemia suggests that intrauterine detection of many metabolic disorders attributed to mutant DNA may ultimately be feasible.

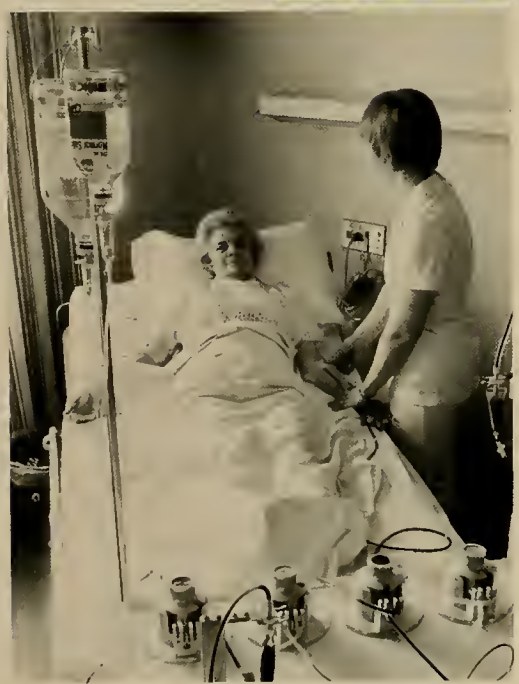
Sickle cell membrane defects. Many of the clinical symptoms of sickle cell anemia, and especially the painful and acute crises, are due to the physical blockage of small blood vessels by the misshapen, elongated, rod-like red blood cells. The tissues and organs ordinarily served by these log-jammed blood vessels no longer receive oxygen and nourishment, nor are metabolic wastes removed from them by a normal circulation.

In recent studies, sickled red blood cells have been found to be more adherent to vascular epithelial cells (which line blood vessels) than are normal red blood cells, regardless of the state of deoxygenation, although no good correlation has been found between severity of the disease and the presence of sickled red blood cells. Experiments with sickled cells and with normal red blood cells have shown that the sickled cells are much more adherent to cultured epithelial cells, which is indicative of a specific membrane defect. Further, there is a strong positive correlation between adherence of the sickle cells and the clinical severity of the disease of patients from whom the cells were derived. Previous efforts tended to concentrate on the structural deformity of the cell due to the rearrangement of the abnormal hemoglobin molecules in rod-like crystals. This new research approach may lead to possible new therapies for sickle cell disease, aimed at the membrane abnormalities of the sickled red cell.

FOUR

LOOKING AHEAD: RESEARCH OPPORTUNITIES AND PROGRAM PLANS

LOOKING AHEAD: RESEARCH OPPORTUNITIES AND PROGRAM PLANS



Faced with the challenge of developing comprehensive, coordinated approaches to a wide range of health problems, NIADDK uses a logical strategy to identify research opportunities and develop program plans that pursue such opportunities. The approach used by Institute planners emphasizes a research program balanced between basic and clinical research, broad participation to determine especially promising research opportunities, and development of experienced research manpower.

Chapter III details recent significant research advances. Since the NIADDK strategy for defining research opportunities and allocating resources to such opportunities focuses on a balanced research program, the opportunities and initiatives reported in the following pages span the full range of scientific activity. This planning process (detailed in chapter VI) endeavors to maintain a rational balance in allocation of funds to fundamental (basic) investigations, clinical studies, and specifically oriented developmental research. Traditionally, the Institute's efforts in support of broad-based fundamental research reflect the recognition that no major progress in treating specific diseases can result without relevant advances in fundamental knowledge. Subsequent clinical and other developmental research then applies such fundamental knowledge to more specific problems.

In using its planning process to identify research opportunities and initiatives, NIADDK places particular emphasis on those opportunities for which results are anticipated in the future. In determining such potential, NIADDK assesses both the state of the science and the availability of research manpower and other resources.

The research opportunities in this chapter have been identified as both promising and needed, by groups that include the National Arthritis, Diabetes, and Digestive and Kidney Diseases Advisory Council; the NIADDK Board of Scientific Counselors; Institute program staff; outside consultants; and the participants in various workshops, task forces, and symposia.

Once research opportunities are identified, NIADDK staff and advisors translate them into specific program plans in any of the following forms:

- **Research grants** to individual investigators and investigator groups to explore a limited range of problems within a specific research category;
- **Clinical trials** to establish safety and efficacy of new treatments in clinical settings;
- **Research contracts** to develop, test, and/or apply more specific procedures, devices, or treatments;
- **Training programs** to maintain an adequate base of qualified investigators;
- **Interagency agreements** that minimize program gaps and overlaps; and
- **Scientific meetings** such as state-of-the-science workshops or consensus conferences.

The following sections describe first key research opportunities and then specific program plans, grouped under each of the four major program headings. Because of the lead time usually required to coordinate, plan, and conduct biomedical research, the initiatives discussed in this chapter are planned for 1982 through 1985.

ARTHRITIS, MUSCULOSKELETAL, AND SKIN DISEASES PROGRAM

RESEARCH OPPORTUNITIES

Chronic Arthritis in Goats Due to a Retrovirus

Caprine arthritis encephalitis is a retrovirus disease of goats that results in a progressive inflammatory arthritis closely resembling rheumatoid arthritis in humans. This disease may be viewed as an animal model of a persistent viral infection causing arthritis, the study of which may be helpful in developing methods for treating or preventing human rheumatoid arthritis. Studies are needed to determine how the virus causes the inflammatory response in joints, whether the immune response is causally involved, and the mechanisms involved in virus persistence and autoimmune responses.

Identification of a Microbial Agent in the Etiology of Arthritis

Lyme arthritis continues to command much attention in the search for an infectious etiology for arthritis. Work is continuing with techniques aimed at identifying a viral or bacterial agent together with attempts to inoculate monkeys to recreate the disease and propagate the causative agent. Further identification of patients through active surveillance and the specification of attack rates within sample human and animal populations are needed. An animal model for Lyme disease must be sought, as well as a description of animal hosts and the natural environment of the implicated agent.

Studies of Microbial Agents As Etiological Factors in Systemic Lupus Erythematosus and Rheumatoid Arthritis

Interest in the possible microbial etiology of SLE and rheumatoid arthritis continues to be high. New and highly sensitive methods are now available for examining tissues from patients with collagen disorders to detect foreign DNA in order to define an etiologic role. Continued pursuit of such studies is particularly timely as the possible role of microbial agents in precipitating an immune response in genetically susceptible individuals has been suggested for a number of diseases; the circumstantial evidence increases the likelihood that such is the case for SLE and rheumatoid arthritis.

Demonstration of Antilymphocyte Antibodies in SLE

Epidemiologic studies demonstrating antilymphocyte antibodies in the sera of household contacts of SLE patients, and even in physicians and technicians working with such sera, are provocative. On the basis of these preliminary findings, the specificity of antilymphocyte antibodies in patients with SLE and their close household contacts needs to be further defined and correlated with fluctuations in disease activity, changes in household living patterns, or other factors.

Genetics of Rheumatic Disease in Children

Research in the Multipurpose Arthritis Centers program is directed at studying the genetic composition of a large group of children with juvenile arthritis. With the recent findings that specific HLA genes are associated with various rheumatic diseases, this area of investigation can now be profitably applied to children. Such studies would enable investigators to determine if the severity of the disease or its specific manifestations are related to a particular HLA-related gene specificity.

Use of Computers in Rheumatic Disease Research

A development of the past several years has been the use of computers in several phases of arthritis center activities, ranging from instruction, to clinical research, to the use of the computer as an automated consultant. These developments indicate that the computer could provide additional benefit by compiling a registry of patients with rheumatologic diseases for use in clinical research. Such a system would enable clinicians and researchers to review experiences with different therapies on large numbers of patients, to accumulate demographic data for use in epidemiologic research in rheumatoid arthritis, and to identify those patients who might profit from educational programs.

Ethnic and Racial Differences in SLE Incidence

A number of recent studies have reported a dramatically higher incidence rate of SLE in Chinese, American black, and certain American Indian women as compared to that in Caucasian American or European women. It has been suggested that sex and race or ethnicity may interact, especially during the reproductive years, placing certain women at risk for the development of SLE. These host factors, in concert with as yet uncharacterized environmental triggers, may be etiologically important. Further studies are warranted, particularly studies of men with SLE, to increase our understanding of the roles of sex hormones in disease predisposition.

Etiology of Osteoarthritis

While the precise cause of osteoarthritis remains undefined, biochemical and mechanical studies are showing increased understanding of pathogenetic mechanisms. These studies indicate that future advances will depend upon continued studies and scientific progress in the evaluation of the effects of prostaglandins and enzymes on cartilage in osteoarthritis, identification of lipid glycoproteins as lubricating agents in synovial fluid, and development of models to explain degenerative processes in joints.

Surgical Revision of Artificial Joints

Joint implants are being placed into younger, more active recipients than in previous years. With earlier artificial joint implantation and a general increase in life expectancy, there are now many patients requiring surgical revision for joint implants that have gradually failed over time. There is a need for research directed not only to surgical revision, but also to such basic concepts as joint surface wear, surface replacements, fixation through cementless bone ingrowth, and long-term biocompatibility. Experience with the current technology for knee and hip joints may facilitate the development of better prosthetic replacements for other body joints.

Genetic Basis for Inherited Disorders of Connective Tissue

New techniques in molecular genetics are permitting a complete description of various stages of connective tissue synthesis within individual cells. In addition, inherited enzymatic defects and new bone proteins have been discovered that may help to elucidate connective tissue metabolism. Rapid advancement of genetic and biochemical assay methods provides additional opportunities for further research and therapeutic gains in many of the inherited connective tissue disorders, such as osteogenesis imperfecta.

Basic Research on Cartilage Transplantation

A major thrust of cartilage transplant research is determining the specific cellular and matrix components of a graft that may produce antigens and lead to graft rejection. New studies of immune suppression directed toward particular antigens which may reduce the incidence of the delayed rejection of implants that has been observed in experimental animals are appropriate now. Studies focusing on the technology for preserving cartilage for future transplant use are also needed.

Improved Therapy in Metabolic Bone Disorders

Accumulating evidence indicates that enhanced bone-forming activity is stimulated by therapeutic doses of fluoride. In one study, a pulsed fluoride regimen resulted in dramatic improvement in postmenopausal osteoporosis. The efficacy and safety of this important treatment for osteoporosis needs to be evaluated in a clinical trial to increase our understanding and improve our ability to treat this metabolic bone disease.

New Application and Basic Mechanisms of Electrical Stimulation

Electrical stimulation techniques developed for fractures that have failed to unite are now being explored for potential application to other bone disorders. Possible applications of this new therapy include treatment of metabolic diseases such as osteoporosis and osteogenesis imperfecta, enhancing bone ingrowth into implants, and reduction of healing time for new fractures. Further basic research is required if we are to understand the molecular mechanisms that are affected by the electrical stimulation.

New Markers and Assays for Bone Studies

A recently identified vitamin K-dependent amino acid of bone allows a new level of sophistication in tracing bone metabolism. Also, new assays for hormones and enzymes and new ultrastructure and electron probe techniques permit investigations into the role of specific substances in the formation and resorption of bone. As a result, imaginative new concepts of molecular regulation can now be investigated.

Research into the Allergic Dermatoses

One of the most compelling areas of research within the field of immunodermatology is the attempt to characterize the role of immune complexes in allergic skin diseases. Assays have been established to demonstrate the presence of immunoglobulins A, G, and M. Researchers are ascertaining the presence of circulating immune complexes in patients with erythema multiforme and Stevens-Johnson syndrome, which in turn may lead to trials of immunosuppressive therapy for these severe and potentially life-threatening disorders.

Research into Oral Retinoids

Recognizing the potential importance of the entire group of aromatic retinoids, the skin diseases program sponsored a workshop on the effect of oral retinoids in dermatologic diseases. The objectives of the workshop were to determine the optimal compound, dose, and period of time of treatment for diseases that are responsive to oral retinoids; to determine the potential side effects of such treatment; and to establish the basis for definitive clinical trials. The results of the workshop indicate that diseases such as psoriasis, ichthyosis, pityriasis rubra pilaris, and Darier's disease may be responsive to oral retinoid therapy, and further studies in these areas are contemplated.

PROGRAM PLANS

Genetic, Immunologic, and Infectious Factors in Rheumatic Diseases

Through existing program mechanisms, emphasis will be given to rheumatoid arthritis, osteoarthritis, arthritis in children, and ankylosing spondylitis as diseases for which genetic factors play an important role and for which infectious agents may be important. Studies to define the roles for cell-mediated immunity and the inflammation that follows the immunological events will also be emphasized, particularly studies comparing responses in children to those in adults. In addition, high priority will also be given to the search for agents involved in the etiology of infectious arthritis.

Rheumatic Disease Workshop

Numerous advances have been made by rheumatologists in the area of immunogenetics, immune complexes, immunopathology, and immunological expression of

rheumatic disease in general, yet understanding of the precise pathogenetic roles of immunological events in these disorders is still incomplete. Two workshops, one on immunogenetics and the other on immune complexes, are planned to promote discussion of what is known in basic immunology as it relates to specific rheumatic diseases and to stimulate research development.

Systemic Connective Tissue Diseases

Certain systemic rheumatic diseases—SLE, polymyositis, scleroderma, and polyarteritis nodosa—require intensive research activity to expand available information about their etiology. While much is known about these diseases, there are many questions remaining. Emphasis will be given to studies in the areas of immunology and genetics, as well as followup evaluations of the efficacy of therapy.

Followup on Health and Nutrition Survey

A resurvey of approximately 5,500 subjects, recently initiated through collaboration with the National Institute on Aging and the National Center for Health Statistics, is expected to provide a rich source of rheumatic disease data relating to changes in previously measured characteristics over time and the association of change and outcome measures.

Arthritis Epidemiology

Formation of an ongoing work group or organization is proposed to provide a forum for further discussion and formulation of specific approaches to the study of arthritis epidemiology. This followup would build on the review of the state of knowledge and identification of research opportunities provided in the Arthritis Epidemiology Conference.

Arthritis Information Clearinghouse

As part of a planned evaluation of clearinghouse products and services, samples of Arthritis Information Clearinghouse products will be submitted to a panel of experts who will assess the products for appropriateness, accuracy, and completeness. Other initiatives may include preparation of an annual cumulative catalog of all materials and services, evaluation of a catalog of patient education materials, development of additional patient education materials, and coordination of allied health education workshops in cooperation with the Arthritis Foundation.

Studies on the Pathogenesis of Low Back Pain

Low back pain, a major disabling disorder, accounts for an expenditure of over $10 billion annually for care and compensation, yet the etiology of back pain is unknown in many cases and the current level of research in this area is very low. The proceedings of a recent workshop on low back pain will be published, and it is hoped that new, high-quality research will be stimulated as a result.

Basic Clinical Studies in Bone Metabolism and Disease

Newly discovered components in bone and bone metabolic markers present great opportunities for productive research. A new clinical trial on the use of fluoride in osteoporosis is expected to produce preliminary and correlative results that may encourage additional studies on bone metabolism. These findings, together with a continued interest in bone diseases, especially brittle bone conditions, and publication of a report of the recent Conference on Heritable Connective Tissue Disorders, are expected to stimulate research in these areas.

Improved Artificial Joints

The number of both initial and revision procedures for artificial joints is rapidly increasing. While the early success rate is high, there is a strong need to improve the long-term prognosis. An NIH consensus development conference on artificial hips, scheduled for March 1982, is expected to provide recommendations for future research direction. The greatest cause of implant failure—fixation problems—will be addressed in a later workshop on interface phenomena.

Sports Activity and Injury

While increasing numbers of Americans are becoming active in sports and fitness programs, few highly meritorious scientific investigations have been generated to study the positive and negative influences of these activities. The musculoskeletal diseases program has recently begun collaborating with the American Academy of Orthopedic Surgery on plans for a workshop to deal with sports activity and injury of the knee, and it is hoped that the published proceedings of this workshop will draw attention to this area of research.

Manpower Development and Other General Activities

In the area of manpower development, efforts to attract young clinical investigators to musculoskeletal disease research will be maintained. A formal evaluation of the musculoskeletal diseases program is scheduled for FY 1982, and program announcements may be generated to encourage research in specific areas targeted by the evaluation. In addition, workshops cosponsored with the American Academy of Orthopedic Surgeons and other government agencies may be planned on timely scientific topics in this area.

Enzymes in Epidermal Disease

As a result of the findings from several laboratories on psoriatic tissue, a program project grant application is being prepared to continue study of certain enzymes found in normal and psoriatic epidermal tissue. The results of such a project may provide insight into the etiology and pathogenesis of psoriasis.

Development of Antibodies to Epidermal Antigens

One of the exciting new areas of current research in skin diseases is the recently acquired ability to produce specific (monoclonal) antibodies to human epithelial cells. Using this new technique, investigators will be able to study the formation of monoclonal antibodies to human epidermal structural proteins, the keratins, and to human epidermal cell membranes. Alterations in antigenicity of keratin and cell surface components in genetic disorders of the epidermis, such as ichthyosis, Darier's disease, psoriasis, and pemphigus, can be examined. A request for applications will be issued to expand activity in this area.

Extension of Study of Original PUVA-Treated Patients

A contract to follow the original 1,300 patients whose psoriasis was treated with PUVA is in its fourth year. In the past year, the 16 cooperating centers reported that patients previously treated with X-ray are at greater risk for squamous cell carcinoma following PUVA. NIADDK plans to continue the monitoring of these patients to determine the incidence of adverse effects associated with this therapy, and a request for proposals will be announced for investigations in this area.

Drugs for Topical Use in Psoriasis

Two years ago, NIADDK concluded a national cooperative study that utilized a double-blind drug screening program to determine the clinical effectiveness of systemic chemotherapeutic agents for topical use in psoriasis. Preliminary results indicated that these agents are effective and no significant toxicity occurred with direct application of these types of drugs to specific lesions on the skin. Proposals for further research on these agents will soon be solicited.

Second NIH Workshop on Vitiligo

To review new research accomplishments in melanocyte-related diseases, NIADDK plans to sponsor a second scientific conference in this area. A consortium grant was awarded to Yale University and five other institutions following the first workshop in 1978, and a conference grant application will soon be submitted for a second workshop, tentatively scheduled for spring 1983.

Workshop on Heritable Skin Disorders

The ability to diagnose heritable disease during early fetal life has made considerable progress. Three percent of the newborn population have some type of birth defect considered to be of primary genetic origin. Thus, a state-of-the-art workshop on birth defects and genetic disorders of the skin is being planned.

DIABETES, ENDOCRINOLOGY, AND METABOLIC DISEASES PROGRAM

RESEARCH OPPORTUNITIES

Etiology and Epidemiology of Diabetes

The identification of precise etiologic factors is a necessary prerequisite for the development of rational and specific measures to prevent diabetes and to interrupt or delay the progressive development of the disease's complications. Epidemiologic research is particularly needed for investigation of the etiology of the various forms of diabetes and for determination of their natural history. Such studies have been highly productive in other diseases, most notably cancer and cardiovascular diseases, and are particularly appropriate now that consensus has been reached on diagnostic criteria for diabetes.

Hormone Biosynthesis, Secretion, and Action

Knowledge of the role of hormones in diabetes is essential to understanding the etiology and pathogenesis of the disease, and in turn to generate new strategies for its treatment and amelioration. Continued efforts are required to refine our knowledge of the detailed molecular processes involved in the synthesis, intracellular packaging, and storage of peptide hormones such as insulin and their exquisitely regulated release in response to specific stimulating substances. Moreover, the continued application of the tools of modern cell biology will provide important insights into the sequence of events involved in hormone action.

Nutrition and Obesity in Diabetes

The importance of nutrition as a key factor in the maintenance of good health and of the role of obesity in the management of chronic diseases, especially non-insulin-dependent diabetes, has received increased recognition in recent years. Current research programs in nutrition and obesity should be broadened to include specific epidemiologic, laboratory, and clinical research into the relationship between nutrition and diabetes.

Role of Blood Glucose Control

Increasing evidence has been accumulated from studies in humans and animals that stricter control of blood glucose may prevent or ameliorate many of the complications of diabetes. The effective transfer of this information to the diabetic patient by trained professionals should greatly enhance the benefits attainable from such biomedical research progress.

Transplantation Studies

The importance of continued efforts in the field of beta cell transplantation is readily appreciated when one assesses the phenomenal impact that either a cure for diabetes or prevention of its complications would provide. To accomplish this during the 1980s, it is essential that continued emphasis be given to defining and overcoming graft rejection, improving the yield and

maintenance of viable pancreatic islets, and examining the impact of islet transplantation on diabetes.

Complications of Diabetes

Advances in the understanding of atherosclerosis and progress in its management will apply to both diabetics and nondiabetics. Elucidation of the reasons for the excess risk in younger persons with diabetes is considered to be of particular importance. Greater interaction among experts in the field of diabetes and atherosclerosis should be fostered to permit better evaluation of hypotheses regarding risk factors. Likewise, there are numerous opportunities to accelerate progress in defining the fundamental pathogenetic mechanisms underlying the evolution of renal disease, diabetic retinopathy, neurological complications, congenital anomalies, and complications of pregnancy in the diabetic person.

Behavioral and Psychosocial Aspects of Diabetes

The nature of diabetes poses some special psychosocial and behavioral research issues that must be addressed. Difficulties in metabolic control appear to be related to a multiplicity of factors including intrinsic metabolic lability, inadequate patient education, and psychosocial stresses. However, sophisticated statistical procedures have been developed to permit complex multivariate analyses which now permit investigators to deal with multiple interactive effects. Further application of these procedures to diabetic populations is indicated.

Studies in Neuroendocrinology and Brain Peptides

About 30 peptides have been found in the central nervous system, many of which appear to have hormone-like effects. Other hormonal peptides, originally discovered in other parts of the body and thought to have actions on other target tissues, are thought also to affect the central nervous system. Unanswered questions about these peptides, including their mechanisms of biosynthesis, release, and interaction with receptors, provide numerous and exciting opportunities for future research.

Mechanism of Hormone Action

Although much progress has been made in the study of hormones, many significant questions still remain. Further investigation is required to elucidate the mechanisms that permit hormones to act on their target tissues but not on other tissues, the nature of their specific effects within these tissues, and the mechanisms by which these effects (and not others) are brought about.

Hormone Interactions

A basic characteristic of endocrine systems is that few, if any, hormone-sensitive processes are regulated by a single hormone. Instead, several hormones appear to work in concert to keep homeostatic mechanisms active. Since the interactions of many hormone systems are poorly understood, studies should be encouraged to define these relationships.

Biogenesis and Fate of Hormones

The endocrinology program has supported studies that have helped to elucidate the pathways by which various hormones are synthesized and produced in the body, as well as studies on the metabolic fate of hormones, presumably after they have exerted their effects. Additional work must be undertaken to understand the processes and ultimate effects of hormonal cleavage, the significance of heterogeneity within hormone groups, and the diagnostic implications of hormone precursor levels.

Biology of Target Organs

Cellular response to hormones depends not only on the amount of circulating hormone available, but also on factors within the cell that influence the nature and intensity of the response. A hormone may produce different actions in different tissues, such as the effects of estrogen in various organs, and the cell response to a hormone may depend on such factors as change in metabolic state, disease, or the age of the cell. Studies of target cells are necessary not only for understanding basic mechanisms of hormone action, but also for understanding and appropriately treating such diseases as postmenopausal osteoporosis.

Hormones and Pharmacotherapy

The use of hormones and related compounds in the treatment of endocrine and other diseases constitutes one of the greatest contributions of endocrinology research to human health. For these gains to continue, major efforts should be devoted to the search for new hormones, the isolation of hormonal factors now known to exist only by virtue of their biological activity, the synthesis of known hormones by either chemical or biological means, the modification of existing hormones to alter their action in a desired manner, and the identification of new agents that can enhance or inhibit the action of hormones.

Treatment of Inborn Metabolic Diseases

Recent advances in purification of human enzymes and encapsulation of enzymes in artificial cells or in "ghosts" of red blood cells have increased research interest in enzyme replacement therapy. Successful replacement of a missing or inactive enzyme will reduce the level of accumulating toxic compounds in the blood or the organs of those with metabolic diseases. Recent breakthroughs in genetic engineering, especially the availability of restriction enzyme technology (essential to the large-scale bacterial production of hormones), may also allow for production of large amounts of active enzymes in bacteria for investigative and eventual therapeutic purposes and should be pursued.

Biochemical Characterization of Cystic Fibrosis

A number of investigators are making progress in isolating, identifying, and characterizing differences between marker substances found in patients with cystic fibrosis and those found in normal individuals. The

nature and behavior of these substances may provide important clues to the basic biochemical defect in CF, thus leading to a potentially more effective treatment of the disease. Moreover, these differences may provide the basis for simple and reliable tests for detecting heterozygote carriers.

Research on the Secretory Process in Cystic Fibrosis

Progress in understanding the secretory process in cystic fibrosis has been made through methods for analyzing the complex glycoproteins that make up mucus, and methods are now available for making increasing amounts of purified CF mucus and normal mucus available to investigators. Similarly, continued progress has been made in methods for studying the anatomy of secretory glands. Further studies such as these show promise for increasing our understanding of the structure and function of these organs and are essential to an understanding of CF.

Noninvasive Methods for Study of Metabolic Processes

Development of powerful modern instrumentation in spectroscopy and chromatography is providing impetus to numerous investigators to expand their instrumental research to **in vitro** study of metabolic processes, three-dimensional imaging of whole organs, and stable isotope studies of metabolism. These techniques could add a new dimension to the study of enzymatic processes and promise to accelerate markedly our understanding of normal and abnormal metabolism.

PROGRAM PLANS

Blood Glucose Control and Long-Term Complications of Diabetes

It has long been recognized that a carefully designed and executed clinical trial is needed to resolve the controversy pertaining to the relationship between the degree of control of blood glucose and the long-term vascular and nervous system complications of noninsulin-dependent diabetes mellitus. In light of significant new technological advances and changes in treatment approaches over the past few years, such a trial is now planned, with considerable promise for successful completion.

Multidisciplinary Diabetes Research

To stimulate and expand investigator-initiated studies in response to the needs and opportunities presented by recent advances in diabetes research, program announcements to solicit grant applications are planned in a number of areas: etiologic factors, pathogenesis, and epidemiology; the role of diet, nutrition, exercise, and obesity; transplantation as a potential treatment approach; animal research models; diabetic nephropathy and cardiovascular, ocular, neurologic, and obstetric and perinatal complications; behavioral and psychosocial aspects; and noninvasive and implantable metabolite sensors for use in diabetes research.

Research Career Awards in Diabetes

The purpose of the special emphasis research career award program is to attract clinically trained individuals to research careers and to provide them the opportunity to acquire experience in selected cross-disciplinary areas. Currently, SERCA programs exist in three multidisciplinary areas of diabetes research: cardiovascular; obstetric, perinatal, and pediatric; and diabetes in the elderly. Expansion of this program to encompass additional multidisciplinary areas, such as immunologic aspects of diabetes, is planned in cooperation with other NIH Institutes. In addition, to evaluate the success of the program, a tracking system will be devised to follow the career development of SERCA holders following the period of award.

Diabetes Centers

Plans are being made to establish additional diabetes centers. To provide support for this expansion, program staff will encourage submission of applications from institutions that appear to be strong potential candidates for centers. In addition, a contract award is planned to support a comprehensive evaluation of the research activities of existing Diabetes Research and Training Centers and Diabetes-Endocrinology Research Centers.

Training in Diabetes Research

Recent research developments indicate important relationships between the onset of insulin-dependent diabetes and the immune system of the individual. Currently, however, there is a virtual absence of investigators who are competent in both diabetes and immunology. To develop a base of training expertise in this area so that investigators with the appropriate cross-cutting skills will be available as soon as possible, a program announcement will be developed requesting relevant national research service award (NRSA) fellowship applications. In addition, to increase the supply of qualified personnel in the epidemiology of diabetes, institutions with extensive ongoing research activities will be contacted for possible submission of applications for NRSA training support. Overall, to assure an adequate supply of trained investigators in the future, a 5 percent expansion in the number of training positions funded through both individual and institutional NRSAs is planned.

Diabetes in the Hispanic Population

In support of the diabetes-related aspects of the National Center for Health Statistics Hispanic Health and Nutrition Examination Survey, NIADDK plans to supplement an existing interagency agreement with that agency. The survey, which is expected to require 2 years for completion and an additional 2 years for data analysis, will provide a wealth of information on diabetes in the Hispanic population.

National Diabetes Communications Programs

A major conclusion of the National Diabetes Advisory Board's national conference on diabetes health services was that many patients could benefit from earlier

application of currently available treatment. Conference members recommended that the authority of NIADDK and its National Diabetes Information Clearinghouse be broadened to include a communications program to disseminate such information. Preliminary plans call for a consensus development project in this area prior to preparation of a request for competitive solicitation.

Endocrinology Research Program Announcement

To keep the endocrinology research program current with identified research opportunities, a program announcement is planned to describe the types of support offered and the scientific emphases of NIADDK's endocrinology program. The announcement will include areas of emphasis developed as a result of a recent evaluation report of research needs in endocrinology and metabolism.

Clinical Applications Workshop

To assure that the results of basic endocrinology research studies are translated as rapidly as possible into clinical practice—for example, the use of hormones as diagnostic tools and hormone interactions in treatment—a workshop on clinical applications of basic endocrine research is planned. The most promising research opportunities identified in the workshop will become the subject of a subsequent request for applications.

Expansion of the Hormone Distribution Program

Plans are being made to negotiate new contracts for the Institute's National Hormone Distribution Program, which will increase the scope of the current program by adding new products for distribution, increase the testing of the products in order to provide uniform standards, and add a product information exchange to the products and services already provided by the NHDP.

Recombinant DNA Production of Hormones

The development of new recombinant DNA techniques capable of replicating both growth hormone and insulin on a large scale provides the potential for producing other peptide hormones by these techniques. The anterior pituitary hormones, such as prolactin, gonadotropic hormones, and thyroid stimulating hormone, as well as parathyroid hormone and the growth factors, are potential candidates. Plans are being made to issue a request for applications and/or a request for cooperative agreement for production of other hormone products by these techniques.

Endocrine Products As Tumor Markers

A workshop is planned in collaboration with the National Cancer Institute (NCI) to discuss the role of prohormones (the precursors of many peptide hormones) and other products of the endocrine system as tumor markers, and to establish whether additional program emphasis should be placed on this aspect of endocrine research. Workshop results may form the basis for a joint effort with NCI to stimulate investigator-initiated applications in this cross-cutting area.

Brain Peptides and Health

There is evidence that peptide hormones within the central nervous system affect such critical functions as hunger and satiety, thirst, body temperature, sleep, memory, mood, and the mediation of pain. However, very little is known of the nature or cellular locus of receptors for central nervous system peptides or the intrinsic mechanisms by which their action is mediated. As a result of a recent workshop sponsored by NIADDK and the National Institute of Neurological and Communicative Disorders and Stroke, a joint program announcement will be published for stimulation of research in this area.

Development of a Special Emphasis Research Career Award in Cystic Fibrosis

Manpower in the area of cystic fibrosis research is known to be inadequate, especially with regard to clinically trained investigators with the knowledge of basic sciences necessary to conduct research on the full spectrum of problems presented by CF. A special emphasis research career award in CF is planned in an effort to interest clinicians in developing research skills early in their careers and to provide them with the opportunity for significant cross-disciplinary experiences.

Cystic Fibrosis Tissue and Materials Repository

The Institute is interested in the initiation of a tissue bank for CF-related material. The National Diabetes Research Interchange, currently being developed by the Juvenile Diabetes Foundation, is similar in concept to the projected CF repository. Plans for the design of such a CF repository will be finalized and a contract awarded, based on the experience gained with diabetes research resources.

Animal Models of Inborn Metabolic Errors

To initiate identification and breeding of animals for study of congenital metabolic diseases, a planning conference followed by a request for proposals is slated for study in the area of inborn errors of metabolism. In many cases, the need for animal models of such disorders is acute, and their limited availability delays progress in identification of treatment methods.

Enzyme Research in Metabolic Diseases

Many of the most exciting research opportunities in the study of metabolic processes focus on enzymes and their actions. To ensure that the program's scope and priorities keep pace with these ongoing developments, a series of workshops is planned to provide state-of-the-art reports on various enzyme-related research areas. These workshops will be followed by one or more program announcements to stimulate research activities in the areas covered by the workshops.

Treatment of Inborn Errors of Metabolism

Some encapsulated adsorbents (e.g., activated charcoal) and enzymes (e.g., catalase) have been tested in animal models of congenital metabolic disorders and were found to be effective in removing toxic substances

from extracellular compartments. A request for proposals is planned to initiate applied therapeutic projects with the objective of testing encapsulated adsorbents and enzymes in selected model systems of inborn metabolic diseases.

Enzyme Replacement Therapy in Metabolic Diseases

Recent advances in animal studies of brain uptake of infused enzymes have contributed to significant progress toward possible elimination of toxic lipid deposits from the brain of patients with Tay-Sachs disease. Still, tissues and organs (e.g., muscle, liver, spleen) remain inaccessible for specific intracellular targeting of active replacement enzymes. Thus, a request for applications is planned to stimulate research in this extremely complex and important area.

Specialized Instrumentation for Metabolic Studies

One of the exciting new areas of current research in metabolic processes utilizes new generations of nuclear magnetic resonance and mass spectroscopy instrumentation. Because of the high cost of these instruments and the highly specialized nature of this research, a request for applications is planned to provide adequate funding without jeopardizing the support of other investigator-initiated research projects in the metabolic diseases program.

Metabolic Studies Related to Reye's Syndrome

As a result of an inter-Institute program announcement including NIADDK, increasing interest on the part of the scientific community is expected in the areas of urea cycle enzymology, lipid metabolism, and hyperammonemia biochemistry as they relate to Reye's syndrome. Increased attention to this problem is vitally important, and NIADDK will continue to devote effort to fostering research in these areas.

DIGESTIVE DISEASES AND NUTRITION PROGRAM

RESEARCH OPPORTUNITIES

Gut-Neural Peptides in Gastrointestinal Function

A number of new biologically active peptides have been found in the brain, the central nervous system, and the gastrointestinal tract. In the gut most of these peptides have been classified as hormones related to the control of the digestive tract and its function; there is considerable speculation about the role of these same or structurally similar peptides in the brain. With the availability of many of these peptides or hormones and assay methodologies, studies should be initiated with the long-term goal of characterizing the actions of gut and brain peptides on the central neural control of the gastrointestinal tract, identifying their mechanism of action, and determining their physiological role in the regulation of gastrointestinal function.

Endoscopy in Gastrointestinal Disorders

Over the past 20 years, endoscopy has developed as a valuable diagnostic and therapeutic discipline in the fields of gastroenterology and surgery. Currently its potential has been demonstrated for the treatment of various disorders of the gastrointestinal tract such as gastrointestinal bleeding, polyps, and gallstones occluding the common bile duct. Similarly, there is potential for the use of endoscopy for basic and applied studies related to the various functions and activities of the digestive tract, such as circulation, motility, and secretion. New biomedical and engineering technology should be exploited and used in conjunction with currently available or newly developed endoscopic instrumentation to enhance research, diagnosis, and therapy of digestive diseases.

Prevention of Bacterial Diseases

It has recently become clear that a number of infectious gastrointestinal diseases are mediated by attachment of microorganisms to the intestinal mucosal surface of the host and subsequent colonization of the gastrointestinal tract. The attached organisms retain the ability to divide and multiply at the surface while resisting being washed away by secretions and by normal peristaltic movements of the intestines. Evidence suggests that, in each case, mucosal adherence is mediated by a specific interaction between surface structures (pili) elaborated by bacteria and receptors on the host mucosal surface. Further research indicates that protection against infectious diarrheas may be possible either by immunizing the individual against the bacterial surface pili or by developing appropriate mucosal surface receptor site analogs to either prevent colonization or dislodge the causative microorganisms from the intestinal mucosal surface of the host. This line of investigation has provided some promising new leads for prevention of a wide range of important bacterial diseases that need to be explored further.

Pathogenesis of Pigment Gallstones

In the United States, many patients who undergo cholecystectomy (removal of the gallbladder) have radiolucent (that is, invisible on X-ray) pigment stones. These stones account for a significant percentage of treatment failures in patients undergoing trials of dissolution of cholesterol gallstones with chenodeoxycholic acid and, thus, are a major health and therapeutic problem. In contrast to the explosion of knowledge concerning the pathogenesis of cholesterol gallstones, progress in pigment stone disease has been slow and not well disseminated. Much remains to be done to elucidate the processes controlling pigment secretion, stone formation and growth, and the role of biliary constituents in preventing precipitation of solids from liquid bile. More basic knowledge is needed before methods for dissolution and prevention of pigment gallstones can be devised. Recent epidemiologic studies demonstrating differences in the incidence and conditions for formation of different types of pigment gallstones may facilitate future investigations.

Prevention of Cholesterol Gallstones

Research in animals has shown that, although bile must be supersaturated with cholesterol to facilitate stone formation, stones do not necessarily form in such bile; other factors are required, particularly "nucleating agents." Possible nucleating agents are mucus and mucous glycoproteins. Much has been learned about the complex glycoproteins, and mucus can not be partially purified and quantitated. Moreover, such agents as aspirin and indomethacin have been shown to inhibit mucous glycoprotein secretion. Therefore, with the demonstration that prevention of mucus production by the gallbladder prevents gallstone formation in animals, a whole new area of investigation has been opened and should see continued exploration.

Progress in Liver Transplantation

The development of more selective, safer immunosuppressive drugs and techniques promises to provide major advances in liver transplantation. The finding that cyclosporin A shows a selectivity against a subpopulation of lymphocytes involved in transplant rejection has been an important step forward; other compounds need to be selectively sought. In addition, the elimination of "passenger leukocytes" from the donor organ by periods of maintenance in tissue culture, such as has been done with pancreatic islet tissue in animal experiments, might be feasible by perfusion with specific drugs. The use of fetal liver tissue and transfusions of blood to the recipient prior to transplantation also appear to make it less likely that the donor organ will provoke an immune reaction. Exciting developments in this entire field invite further research.

Basic Studies on Liver Cell Function

A number of significant technological advances have occurred in recent years, enabling scientists to probe the functions of hepatocyte membranes where disturbances impair the normal process of bile formation. There are now research opportunities to apply and improve current techniques for separation of the liver cell plasma membrane to provide a better understanding of the structure and function of the liver cell in health and disease.

Cirrhosis of the Liver

Research in model systems other than the liver is providing information on the regulation of connective tissue substances; the role of collagenases, which break down collagen; and the role of mediators formed by lymphocytes and monocytes that stimulate abnormal connective tissue growth. These approaches now need to be applied to the study of excess connective tissue formation in cirrhosis of the liver.

Immunology and Liver Disease

Immunological mechanisms appear to play a role in two important liver diseases (primary biliary cirrhosis and autoimmune chronic active hepatitis), and advances in basic immunological techniques need to be applied to the study of these diseases. Investigations required include development of animal models of the human diseases, characterization of the potential autoantigens, and development of improved **in vitro** and serological assays. These types of basic research investigations of immunological phenomena may lead to a better understanding of the pathogenesis of these diseases and methods for immunologic modulation.

Peroxisomes and Obesity

Peroxisomes (enzymes isolated from mitochondria) may be the active sites of heat production and important in the prevention of obesity. Recent studies show that these compounds are increased several-fold under conditions that increase brown fat (e.g., cold and high-fat diets). The regulation of peroxisomes offers great promise in the regulation of energy balance and thus (indirectly) obesity, and additional research in this area is indicated.

Leucine Metabolism

A number of studies involving branched-chain amino acid metabolism suggest that leucine or its analogue, alpha keto isocaproic acid (KIC), has a regulatory effect on protein turnover and synthesis. This property does not appear to be due to its recognized role as an essential amino acid; moreover, the other branched-chain amino acids (isoleucine or valine) and their corresponding analogues do not appear to have such an effect. The finding that leucine and KIC influence protein conservation in muscle and protein synthesis may offer real promise in metabolic studies on diabetes, portal-systemic encephalopathy, trauma, and renal disease.

Factors Affecting Human Nutrient Requirements

Environmental and host factors that affect the utilization of and requirement for essential nutrients need to be studied. Included among these factors are environmental and/or physiological stress, physical activity, medication, and disease states (diarrheal disease, parasitism, and chronic infection). Limits of adaptation to low intake of essential nutrients and the consequent health effects need to be better defined. This area of research, which is especially relevant to conditions found where families are living in poverty, includes studies on nutrition and disease-nutrient interactions, bioavailability, and nutrient absorption and utilization. In addition, the extent to which chronic malnutrition may interfere with (or augment) host-defense immune mechanisms is not known and much additional research in this area is needed.

PROGRAM PLANS

Clinical Trial for Endoscopic Control of Upper GI Bleeding

During the past 5 years, research and development efforts have resulted in a number of methods that can be used in conjunction with the fiberoptic flexible endoscope for the control of upper gastrointestinal bleeding. These include laser photocoagulation, tissue adhesives,

thermal probes, and several different modes of electrocautery. To provide adequate data on the efficacy and safety of these procedures, a multicenter, controlled clinical trial is planned. Preliminary evidence suggests that some of the methods may hold great promise for therapy of upper gastrointestinal hemorrhage.

Bacterial Adhesion and Infectious Diarrheas

Much recent knowledge has been assembled related to the attachment of microorganisms to the intestinal mucosal surface and its relationship to the pathogenesis, prevention, and treatment of infectious diarrheas. To update and evaluate this present knowledge and to suggest further avenues of productive research, a workshop is planned to bring together microbiologists, gastroenterologists, morphologists, biochemists, and physiologists actively pursuing research in the area.

Pancreatic Disease

Pancreatitis remains a puzzling disorder with diagnosis and therapy that are both nonspecific. However, many of the basic studies on the cell physiology of protein synthesis, packaging, and secretion have been carried out on pancreatic acinar cells. Therefore, program announcements or requests for applications will be initiated to ensure that this fundamental information on the biology of the pancreatic cell is pursued in such a way that it can be applied to the diagnosis, treatment, and prevention of pancreatic disease and elucidation of its pathogenesis.

Pigment Gallstone Disease

Studies of the pathogenesis, diagnosis, prevention, and treatment of pigment gallstone disease are the focus of a number of program announcements or requests for applications being planned by the Institute. Support is intended for collaborative research between investigators with expertise in bilirubin chemistry, biochemistry, physiology, physical chemistry, gallstone disease, crystal formation and growth, epidemiology, genetics, radiology, and calcium and protein metabolism.

Cholesterol Gallstone Formation

NIADDK plans to develop a comprehensive, multidisciplinary program to investigate new methods to prevent the formation of cholesterol gallstones in individuals at high risk for the disease. In addition, epidemiologic studies of the incidence of gallstones in patients taking large doses of aspirin or indomethacin, such as individuals with rheumatoid arthritis, will be encouraged. Ultimately, if warranted by the research findings, a clinical trial will be developed in which a population at high risk for the development of stones, such as American Indian women, will be placed on prophylactic therapy for comparison with a no-treatment group.

Publication and Evaluation

To increase its education and information activities, the National Digestive Diseases Education and Information Clearinghouse plans to produce additional fact sheets each year. The clearinghouse staff also plans to determine what additional materials and services are needed besides those currently available from digestive diseases organizations, drug companies, and government agencies.

Expansion of the CNRU Program

To increase clinical nutrition research and training and to upgrade the use of nutrition knowledge in clinical practice, a program announcement is planned to establish additional clinical nutrition research units during the next several years.

Methods for Characterizing Obesity

Most clinical studies of obesity fail to differentiate one type of obesity from another, since no physiologically valid and clinically applicable classification system exists. Using the outcomes of a scientific workshop, NIADDK plans to test a set of proposed classification methods in a cooperative pilot study of a diverse group of self-selected and referred obese patients. Those methods found to be important and clinically suitable will be described for publication in a manual of methodologies for characterizing obesity.

KIDNEY, UROLOGIC, AND BLOOD DISEASES PROGRAM

RESEARCH OPPORTUNITIES

Perfusion of Isolated Glomeruli

Using a newly developed technique of isolated glomerular perfusion, investigators should be able to study the effect of pharmacologic agents on glomerular dynamics and to measure directly glomerular filtration in normal and disease states. The most important use of this technique may be for the study of the immunologic basis of renal disease, especially the mechanisms involved in the deposition of immune complexes within the glomerulus. Once the characteristics (size, shape, and charge) of deposited complexes are determined, pharmacologic agents may be studied to assess their potential for modifying the process.

Drug Therapy in Dialysis Osteodystrophy

The drug 1,25 dihydroxyvitamin D (1,25) has been used in the treatment of secondary hyperparathyroidism in patients with chronic renal failure. Despite research advances and the broad utilization of 1,25, problems of hyperparathyroidism and hypercalcemia in some patients persist. An important issue to be considered is the utilization of an alternative drug (24,25 dihydroxyvitamin D) as a pharmacologic agent in the uremic model to prevent or to alleviate dialysis osteodystrophy resulting from hyperparathyroidism. This vitamin D metabolite might help not only in the intestinal absorption of calcium with secondary improvement in bone mineralization, but also as a research tool to further define the role of vitamin D in the uremic patient.

Plasmapheresis in Patients With Severe SLE Glomerulonephritis

One of the major causes of the morbidity and mortality resulting from systemic lupus erythematosus is renal involvement, leading to the grave complication of lupus nephritis. This is an important area of investigation since lupus nephritis carries with it a high risk of progression to end-stage renal failure as well as a high mortality rate. Anecdotal data suggest that cleansing of blood plasma by plasmapheresis may benefit these patients. Because of this evidence and the magnitude of cost associated with end-stage renal disease treatment, a clinical study of plasmapheresis appears justified.

Continuous Ambulatory Peritoneal Dialysis for Chronic Renal Failure

Continuous ambulatory peritoneal dialysis, a new type of peritoneal dialysis, is a continuous treatment—24 hours per day, 7 days per week. Current and planned investigations seek to improve the therapeutic technique, evaluate the long-term outcome, compare results with those of hemodialysis, and assess its metabolic effects. Investigations are in progress to evaluate potential improvements in sterile techniques and options for the management of potential complications such as peritonitis.

Improvement in Graft Survival

The importance of HLA-DR matching (tissue typing) in transplanting cadaver kidneys has become increasingly emphasized in an effort to improve the survival rate of grafts, and the chronic renal disease program currently supports studies in this area. Broader confirmatory studies of the usefulness of HLA typing in improving graft survival are needed and are of particular importance in the highly genetically diverse U.S. population.

Long-Term Culture Techniques for Hematopoietic Stem Cells

Development of long-term culture techniques for hematopoietic (blood-forming) stem cells has made it possible to study the interaction of the various components of hematopoietic differentiation, as well as offering a possibility of improving bone marrow transplant techniques. At present, very precise matches are necessary to avoid graft versus host disease, limiting the usefulness of the technique. Further studies of this technique and its potential clinical application may be important in the treatment of numerous diseases ranging from Cooley's anemia to leukemia.

Bone Marrow Stem Cells

The development of powerful new techniques makes it possible to alter the genetic makeup of precursor blood cells. These genetically engineered stem cells can be transplanted back into an animal host and allowed to differentiate, and their progeny examined for study of the genetic alterations. In this way, much valuable information about the mechanisms of genetic regulation can be obtained, and new possibilities for research on hemoglobinopathies and other genetic diseases may emerge.

Molecular Defects in Hemoglobinopathies

There is an opportunity to define precisely the various molecular defects responsible for different forms of thalassemia and other related hemoglobin disorders. Knowledge about the structure of the molecular genetic system and cloning techniques has improved significantly, and with this information the structural and functional basis of thalassemia may be elucidated.

PROGRAM PLANS

Shift in Emphasis of Nephrology Training

Recommendations have been made for shifting the direction of training in nephrology research from the conventional emphasis on renal physiology toward studies of renal immunology, biochemistry, and genetics. Analyses of trends in research and the advisability of changing the research emphasis in training are being contemplated for future action.

Research in End-Stage Renal Disease

To increase investigator-initiated research grants related to the study of end-stage renal disease, a combination of workshops and published proceedings, followed by a request for applications for each subarea, is planned. Working groups and workshops are anticipated in the following areas: congenital and genetic causes of renal disease; diabetic nephropathy; kidney transplantation; and unsolved problems and complications of maintenance therapies.

Immunologic Studies of Chronic Renal Failure

Several phases of implementation of studies in immunology of chronic renal failure are planned, including study of disease causes, treatment of the diseases, and prevention of kidney transplant rejection with immunosuppressive therapy. The first phase would consist of funding investigator-initiated basic research in the immunopathology of renal disease. The second phase would involve development of relevant multidisciplinary centers. Subsequent phases of the implementation of studies in renal immunology would include careful identification and classification of renal disease, definition of a population for controlled clinical trials, and identification of new types of immunosuppressive treatments for renal transplantation.

Benign Prostatic Hyperplasia

Benign prostatic hyperplasia is an almost universal phenomenon in aging men, with recent studies suggesting a prevalence in excess of 80 percent in males over age 40. The morbidity attributable to bladder outlet obstruction due to enlargement of the prostate, and to consequent infection of the urinary tract and renal dysfunction, is widespread. As a prelude to initiating a request for applications or a program announcement related to benign prostatic hyperplasia, a workshop/conference is planned which will focus on research

progress not only in the area of the prostate gland, but also in relevant endocrine, metabolic, and other related disciplines involved in prostate research.

Vitamin B_{12} and Folic Acid

Numerous questions about human health in relation to vitamin B_{12} and folate need to be answered. These questions include how the substances are absorbed and transported, how they interact, why folate deficiency is so widespread throughout the world, and why vitamin B_{12} deficiency develops in circumstances where it would not be expected. A request for applications will be published to stimulate interest and activity in these areas.

Research on Erythropoietin Production and Action

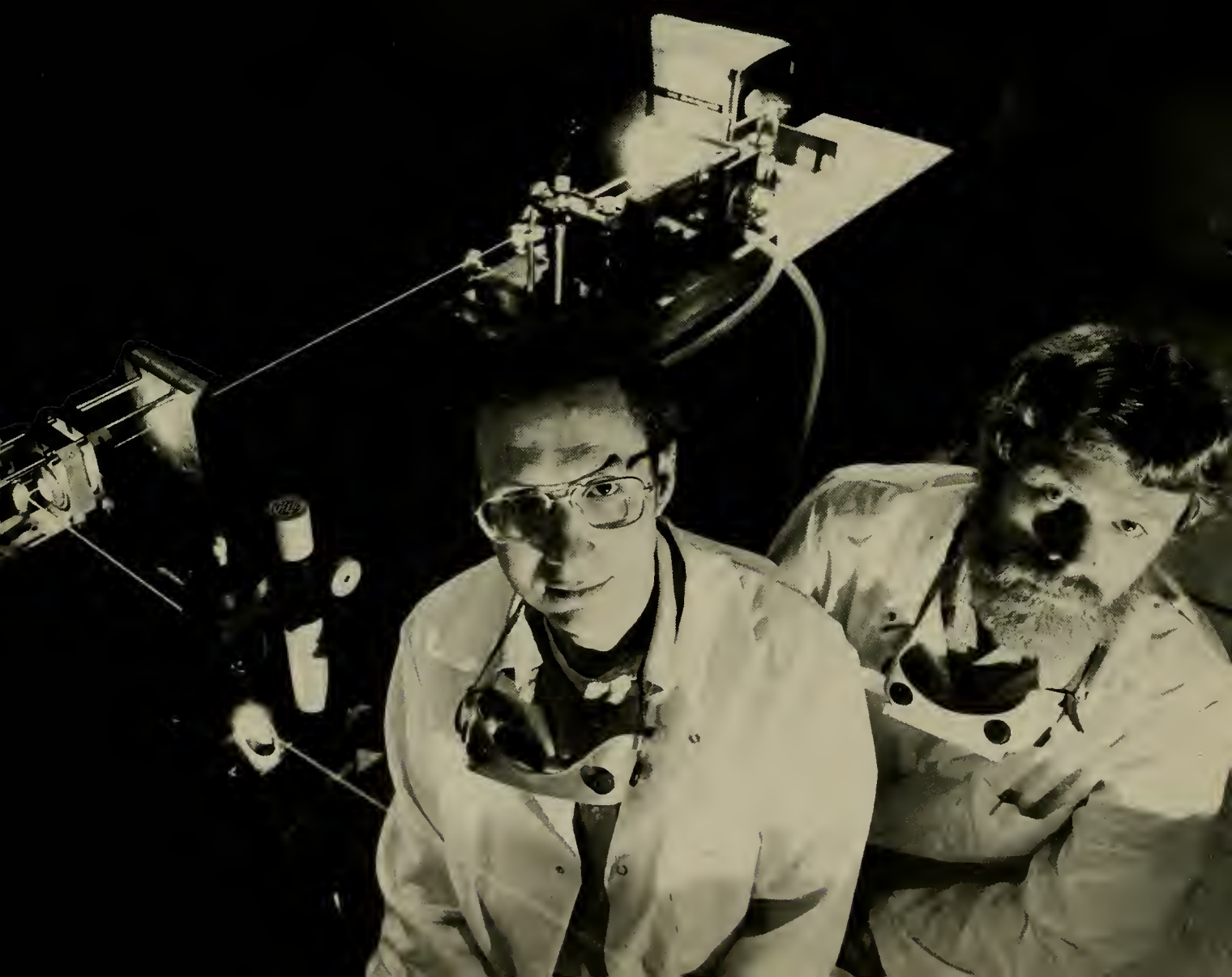
Recent developments have led to the potential for abundant production of erythropoietin, a stimulant for red blood cell production. A shortage of this hormone currently impedes much-needed research studies. Its increased availability is expected to have a significant impact on laboratory research as well as on clinical studies, such as the use of erythropoietin to counteract the anemia of chronic renal failure. A program announcement is planned to stimulate research studies in the area of erythropoietin synthesis and action.

Red Cell Membrane Structure in Normal and Diseased States

Further study of normal and abnormal red cell membrane structure and function is one of the most pressing areas for future research in hematology. Some of the more important problems include the effect of exogenous substances or conditions on red cell shape; the degree and mechanisms of membrane fluidity maintenance in transport, enzyme function, and membrane integrity; mechanisms of red cell hemolysis associated with oxidant damage to membrane lipids and proteins; and fragility of membranes in spherocytic hemolytic anemia associated with spectrin deficiency. A program announcement will be issued to solicit research applications for study of these aspects of the red cell membrane.

FIVE

SUSTAINING PROGRESS: RESEARCH MANPOWER DEVELOPMENT



Photographs

Preceding page—NIADDK scientists

Page 91, from top—[illegible]; field studies; white blood cell, computer simulation

Photo [illegible]

SUSTAINING PROGRESS: RESEARCH MANPOWER DEVELOPMENT

Since its creation in 1950, NIADDK has had a tradition of supporting the training and development of skilled research investigators for service in the areas within its mandate. A high Institute priority has been to ensure that an adequate pool of talented investigators is available to sustain and expand progress in these biomedical research areas. The goal of this effort, over time, has remained constant: to develop the investigator base necessary for meaningful basic research, rigorous clinical testing and validation, and diffusion of research findings to the practicing health care community.

The most effective way to assure that an adequate pool of talented investigators is available is to formulate and maintain a research manpower development program that will provide a range of mechanisms designed to fit the needs of motivated future investigators. Several recently initiated mechanisms, such as the new investigator research award, the clinical investigator award, the national research service award senior postdoctoral fellowship, and the special emphasis research career award, will contribute markedly to the Institute's ability to attract talented scientists and prepare them for research careers. The Institute also encourages the development of short-term training programs to enable medical students to gain experience in research during summer breaks.

There is a serious concern, however, that an increasing shortage of trained investigators, as well as severe budget constraints in most researcher training programs, will limit the availability of research manpower to build upon the advances of the recent past. The decreasing number of physician-researchers and a shortage of trained epidemiologists in particular are cause for growing concern, but the problem exists at all levels and in all research specialties.

Because one common element of all NIADDK components is the continuing critical need for increases and improvements in available manpower, each of the categorical disease programs will continue to use, to the extent possible, the training and development mechanisms described in this chapter. In addition, certain disease-specific training efforts with a strong potential for success will be emphasized in the coming year.

TYPES OF TRAINING AWARDS

The nature of the training mechanisms used by NIADDK has changed over time, evolving to meet the needs of the biomedical research system. Currently NIADDK is making major efforts to provide professional training of researchers for all four of its major disease areas. Figure 3 shows the distribution of the types of training awards among the programs of the Institute.

NATIONAL RESEARCH SERVICE AWARDS

The national research service awards provide for the training of biomedical and behavioral scientists in areas of national need. NRSAs can be in the form of individual postdoctoral fellowships or institutional training grants. After completing NRSA-supported training,

recipients are expected to engage in biomedical or behavioral research or teaching for a period equal to the period of support. If an individual fails to fulfill the service or "payback" obligation, or if appropriate opportunities are determined to be unavailable, the Federal Government is entitled to recover the stipend the individual received from NIH.

Individual Postdoctoral Fellowships

Individual NRSAs are made to applicants who have received a Ph.D., M.D., or equivalent degree for postdoctoral research training. The award provides the opportunity to carry out supervised research to enable biomedical scientists, clinicians, and others to broaden their scientific backgrounds and expand their potential for research in health-related areas. Before applying, each applicant must arrange to work with a sponsor affiliated with an institution having the staff and facilities needed for the proposed training. Federal laboratories, such as those of NIADDK's intramural programs, as well as universities, medical schools, research hospitals, and similar public or private institutions are among the eligible organizations, and recipients are selected through national competition. Annual stipends are determined by the applicants' number of years of relevant postdoctoral experience, such as industrial research, teaching, internship, and residency. Sponsoring institutions may request and receive an institutional allowance for each trainee's tuition, fees, and related costs, such as research supplies and equipment, travel to scientific meetings, and medical insurance.

Institutional Training Grants

An institutional NRSA may be awarded to a domestic public, nonprofit private, or Federal institution to support a training program in a specific area of research. In most instances, institutions may request support for both pre- and postdoctoral trainees. The applicant institution must have, or be able to develop, the staff and facilities required for the proposed program and is responsible for selecting trainees. Predoctoral trainees must have received an appropriate baccalaureate degree, and individuals at the postdoctoral level must have received a Ph.D., M.D., D.D.S., D.V.M., or equivalent degree. The stipend for predoctoral trainees is a fixed sum; for postdoctoral trainees the stipend is determined by a schedule that takes into consideration the number of years of relevant postdoctoral experience at the time of appointment.

The applicant institution may also request tuition, fees, and travel costs for trainees, as well as an allowance to cover such items as partial salaries of faculty and other staff members involved in providing the training, equipment, and supplies. Institutional grants may be made for periods of up to 5 years and may be renewed; however, no individual may receive more than 8 years of support (5 years predoctoral, 3 years postdoctoral) unless a waiver is granted by NIADDK.

Figure 3.—Types of training awards used by NIADDK programs

Programs	National Research Service Award (NRSA)-Individual	National Research Service Award (NRSA)-Institutional	Clinical Investigator Award (CIA)	New Investigator Research Award	Research Career Development Award (RCDA)	Special Emphasis Research Career Award (SERCA)	Minority Biomedical Support (MBS)
	Training Awards *						
Arthritis	✓	✓	✓	✓	✓		✓
Musculoskeletal Diseases	✓	✓	✓	✓	✓		✓
Skin Diseases	✓	✓	✓	✓	✓		✓
Diabetes	✓	✓	✓	✓	✓	✓	✓
Endocrinology	✓	✓	✓	✓	✓		✓
Metabolic Diseases	✓	✓	✓	✓	✓		✓
Digestive Diseases	✓	✓	✓	✓	✓		✓
Nutrition	✓	✓	✓	✓	✓		✓
Kidney and Urologic Diseases	✓	✓	✓	✓	✓		✓
Blood Diseases	✓	✓	✓	✓	✓		✓

*See pages 91-94 for detailed descriptions of each type.

Short-Term Training for Students in Professional Schools

NIH has recently initiated a program to provide research experience for talented students in professional schools. The program is designed to help prevent a future shortage of clinical investigators by attracting highly qualified professional students to careers in biomedical and behavioral research. Domestic schools of medicine, osteopathy, dentistry, veterinary medicine, optometry, pharmacy, and podiatry may apply for grants to support short-term research training for their students for discrete periods of up to 3 months. Only one application for such a program per professional school can be accepted. Research training support for these short periods is not subject to NRSA payback requirements.

The training institution is responsible for appointing trainees who have successfully completed at least one semester at an accredited school of biomedical/behavioral sciences prior to participating in the program; however, NRSA awards cannot be used to support courses that are required for the M.D., D.O., D.D.S., D.V.M., and other similar professional degrees.

Senior Postdoctoral Fellowship

Investigators who have held the doctorate for at least 7 years may apply for a senior postdoctoral fellowship. These awards are intended to provide more established investigators with the opportunity to broaden their scientific background and expertise in health-related research. The award provides a stipend for the investigator, and sponsoring institutions may request an allowance to cover the trainee's tuition, fees, and related costs, such as research supplies and equipment, travel to scientific meetings, and medical insurance. A senior postdoctoral fellowship is usually awarded for 1 year, is subject to NRSA payback requirements, and may not exceed 3 years' total support unless a waiver is granted.

CLINICAL INVESTIGATOR AWARD

The clinical investigator award (CIA) is directed to clinically trained individuals with demonstrated aptitude in research and provides them with the opportunity to develop into independent biomedical investigators. Offering salary support as well as fringe benefits, the CIA program specifically seeks to develop research ability in individuals with clinical background and training. Three years of salary support and a limited budget for research expenses are provided. This award is intended to provide research support in the transition between fellowship or trainee experience and a career in independent investigation.

NEW INVESTIGATOR RESEARCH AWARD

To help bridge the transition from training status to that of established investigator, the new investigator research award provides funds for relatively inexperienced investigators with meritorious research ideas. The award is designed to encourage the development of research interests and capabilities among both new investigators and those who have interrupted early promising research careers.

This special program provides 3 years of nonrenewable research grant support for the initial independent research efforts of new investigators. Eligibility for this program is limited to those who have been awarded a doctoral degree (or the equivalent) within 5 years of the time of the award, and who have not been named previously as the primary recipient of a Public Health Service-supported research grant or contract award except for a fellowship or traineeship.

RESEARCH CAREER DEVELOPMENT AWARD

The research career development award (RCDA) is a special grant awarded to an institution for support of a named individual. The RCDA provides salary and fringe benefits for 5 years, so that the awardee investigator may be relieved of teaching and administrative duties and pursue research interests full time. The goal of this program is to provide opportunities for enhancement of the research capabilities of individuals in the formative stages of their careers who have demonstrated outstanding potential for contributing as independent investigators to health-related research. The awards are available for persons whose research potential is apparent but who need additional experience in a productive scientific environment conducive to the development of a career in independent research. The RCDA is not intended for the untried investigator or for those already established as independent investigators. Neither is the award intended simply to substitute one source of salary support for another for an individual who is already conducting full-time research or as a mechanism for providing institutional support.

SPECIAL EMPHASIS RESEARCH CAREER AWARD

Special emphasis research career awards are offered in three areas of diabetes research:

- Cardiovascular, endocrinologic, and metabolic aspects;
- Obstetrical, neonatal, and pediatric aspects; and
- Diabetes in the elderly.

These three awards are sponsored by NIADDK in conjunction with the National Heart, Lung, and Blood Institute, the National Institute of Child Health and Human Development, and the National Institute on Aging, respectively. The SERCA provides the opportunity for clinically trained individuals with developing research interests to acquire experience and skill in the broad fundamental and clinical scientific disciplines essential for a multidisciplinary approach to the study of these selected aspects of diabetes mellitus. In contrast to other NIH awards, which encourage the development of skills in a single discipline within a single laboratory, this award emphasizes in-depth experience in several fundamental and clinical scientific disciplines that are not necessarily dependent upon a single laboratory or institution.

The SERCA is intended to encourage qualified individuals in the early stages of their postgraduate medical and scientific careers to develop research interests and skills in particular aspects of diabetes mellitus, to provide 5 years of salary support and limited amounts for research expenses to enable individuals to pursue a program of research in various fundamental and clinical research disciplines related to diabetes mellitus and its sequelae, and to create a pool of highly qualified investigators with experience and skills in these selected areas of diabetes research for future roles in related areas of research.

Candidates for the SERCA must meet two basic requirements: (1) an M.D. or equivalent professional degree (e.g., D.D.S., D.O., D.V.M.) and (2) a minimum of 3 years' post-M.D. experience, including 1 year of clinical training in an appropriate subspecialty or 2 years' post-M.D.-Ph.D. experience or equivalent. M.D.-Ph.D. applicants must possess significant experience in metabolism, endocrinology, physiology, biochemistry, pharmacology, or other relevant areas of interest, such as epidemiology.

MINORITY PROGRAM SUPPORT

NIH has several programs that provide opportunities for members of ethnic and racial minority groups to enter the mainstream of biomedical research. These programs seek to strengthen the capability of minority colleges and universities to conduct research, motivate and prepare undergraduate students for advanced studies, and provide research training in biomedical science for faculty and graduate students. In 1977, NIH initiated the NIH Extramural Associates Program to familiarize minority and women's colleges and universities with NIH research activities, thus enhancing their capabilities to participate in NIH-supported health research.

NIADDK contributes to the support of minority colleges and universities through the NIH Minority Biomedical Support (MBS) Program of the Division of Research Resources. NIADDK reviews and funds meritorious MBS applications that are consistent with its mission and program objectives and maintains a close working relationship with MBS staff and individual grantees.

PROFESSIONALS IN EPIDEMIOLOGICAL RESEARCH

Epidemiological research can result in improved early detection, diagnosis, treatment, and prevention of the chronic diseases within the scope of NIADDK. In many cases, it is invaluable in elucidating the specific etiology of a disease. Progress in epidemiologic studies, however, has been severely restricted because the number of professionals trained in pertinent fields is insufficient to carry out needed research programs.

To correct this deficiency, formal training of epidemiologists should include field and survey design experience and execution as practiced by the National Center for Health Statistics. Trained epidemiology investigators are needed to collaborate with the research, education, and community programs of the arthritis and diabetes centers.

Recruitment strategies are needed to encourage young physicians to commit themselves to epidemiologic research. In a 2-year program, they could acquire epidemiologic skills but would not necessarily be enrolled in a program leading to a specific degree. Such training could be acquired within one of the NIADDK-supported arthritis or diabetes centers.

Formal university-based degree programs need to be emphasized as the primary source of professional epidemiologists, who may or may not be physicians. However, the schools that are equipped to offer the desired training in chronic disease epidemiology in the diseases within NIADDK's responsibility, in most instances, lack a senior staff member with competence or interest in field research, which is an essential component of training in epidemiology. These schools require support beyond that needed for merely the academic program. Substantial grants-in-aid are needed for faculty and student support.

In addition, young physicians, who may be undertaking their postgraduate training, will be needed to participate in research in the various proposed Federal epidemiology projects. These young physicians should be recruited as soon as possible to gain needed field experience by participating in and conducting epidemiology research projects at the Centers for Disease Control (Atlanta) and the National Center for Health Statistics, both of the Public Health Service, or NIADDK center and field studies units, the Veterans Administration, or other proposed epidemiology units.

Recognizing the importance of epidemiology to a comprehensive national effort in arthritis, NIADDK established an arthritis epidemiology program office in 1978. This office has collected data and mobilized resources as first steps in preparing a report on arthritis epidemiology, which will include a literature review and state-of-the-art assessment. In addition, a report on epidemiologic activities of the Institute's Multipurpose Arthritis Centers is in progress, and a workshop on arthritis epidemiology was planned for fiscal year 1980.

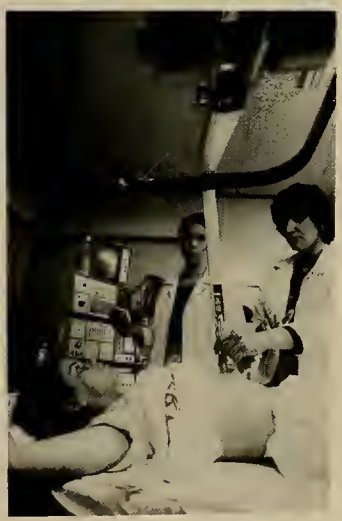
The primary objective of these and other efforts is to encourage epidemiologic research on the distribution, natural history, and risk factors associated with rheumatic diseases—promising research that can be pursued only with an adequate base of epidemiologists knowledgeable in this disease area.

NIADDK has also initiated discussions with several well-established diabetes research centers regarding development of epidemiology training programs. In September 1978, eight Institutes issued an NIH-wide program announcement soliciting applications for epidemiologic research and training. The number of applications received has been encouraging, but it remains clear that epidemiologic study of diabetes should still be expanded. The new program announcement stresses the fact that there are many needs and opportunities for epidemiologic research in diabetes.

SIX

RESPONSIVE STEWARDSHIP: PROGRAM PLANNING AND EVALUATION

RESPONSIVE STEWARDSHIP: PROGRAM PLANNING AND EVALUATION



The diversity of categorical research responsibilities of NIADDK, the prevailing lack of precise knowledge concerning the causes of many of the diseases under study, the constantly changing (but always advancing) state of the art in the different biomedical disciplines, the need to funnel support to special areas where recent progress calls for rapid exploitation of new scientific opportunities—all these make it imperative that the Institute leadership be able to respond actively to evolving changes in biomedical knowledge. Simultaneously, it is incumbent on the Institute leadership to maintain stability of support wherever feasible and where rational long-range research goals are being pursued. Such a course of action calls for a constant, combined process of program overview, evaluation, and planning, and perforce must involve the best available consultative scientific talent both inside and outside the Institute. It must also be accompanied by continuous two-way communication with the Congress, the scientific community, and the interested public to maintain the confidence of these constituencies in a diverse and uncharted undertaking in which the only predictable, constant feature is change.

APPROACHES TO PLANNING AND EVALUATION AT NIADDK

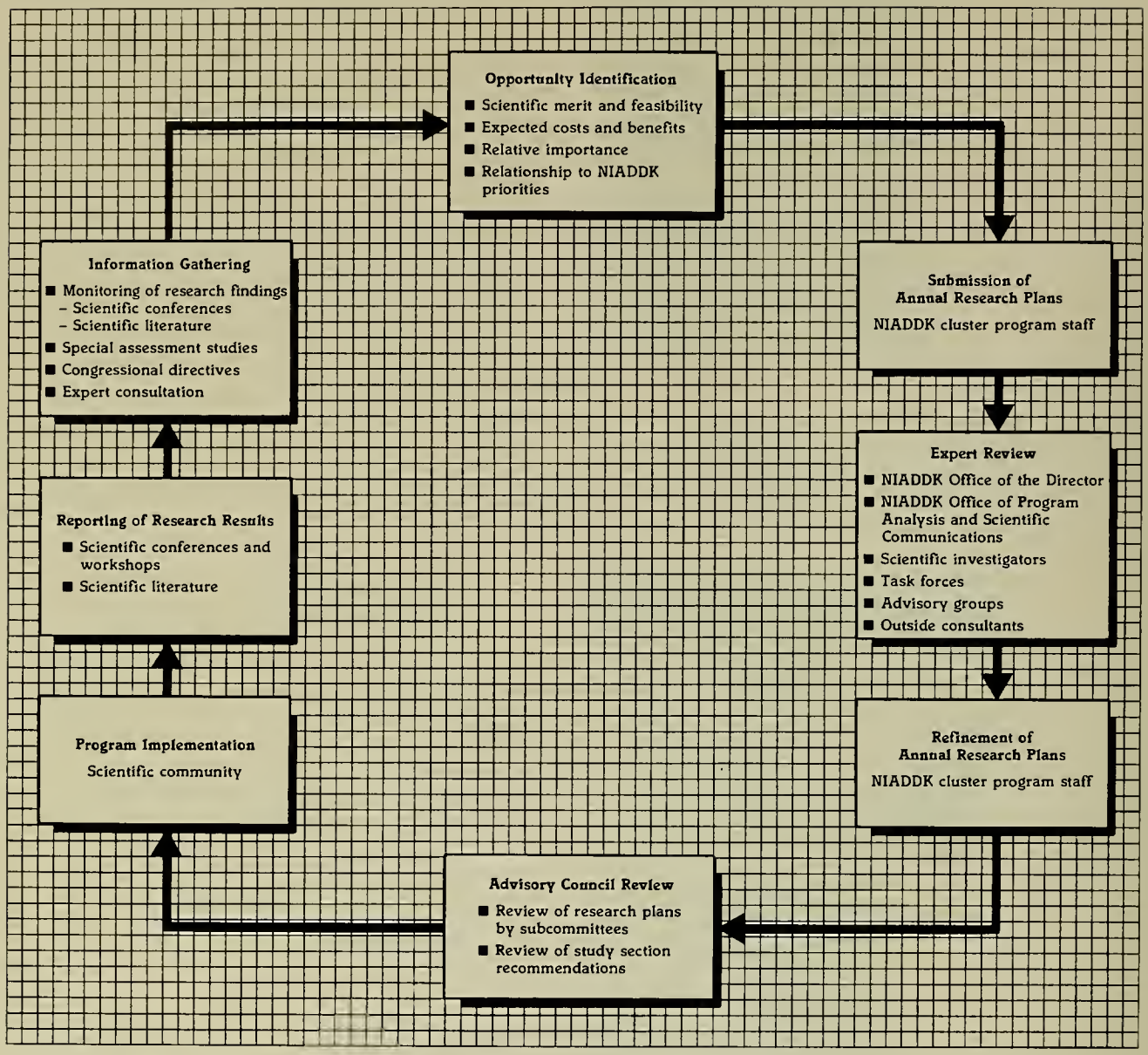
The planning process used by NIADDK for determining the course of ongoing efforts and plotting new research directions is purposely molded to take into account the diverse, though intricately related, scientific issues inherent in biomedical research. Unlike other types of planning, in which contributing factors may be static or at least highly predictable, research planning does not take place in an atmosphere of certainty: The sources of requisite data are far from limited; the state of knowledge changes constantly—both advancing and expanding; relationships among new findings are often not immediately obvious; and the timeframe within which new research achievements will occur cannot be predicted consistently.

While NIADDK's planning and evaluation strategy is extremely broad-based, it nonetheless retains a central focus. Specific scientific goals are set and data are sought and reviewed by multiple bodies of experts. The Institute's various program staffs carefully monitor and interrelate events that affect scientific progress; special studies are undertaken in problem areas; objectives are periodically formulated and revised; and the NIADDK leadership weighs administrative decisions in light of well-defined research opportunities and the resources available. The major steps in this complex process and the primary mechanisms utilized by NIADDK are illustrated in figure 4.

PLANNING

The planning process is based on a series of steps involving information gathering, progress assessment,

Figure 4.—Annual NIADDK planning cycle: steps and mechanisms



opportunity identification, and expert review. The Institute gathers information by consulting experts in the scientific community, through a variety of special planning and evaluation studies, and by careful monitoring of progress in ongoing research.

Since NIADDK relies heavily on investigator-initiated research, new opportunities must be explored by the scientific community for development of implementation methods. Thus, NIADDK publicizes information concerning the scientific challenge of new opportunities or emerging research objectives through broadly disseminated announcements in the NIH "Guide for Grants and Contracts," organization of scientific conferences and workshops, publications, and other means. These actions usually prompt a positive reaction in the scientific community, and individual investigators respond to information about new directions of high priority to NIADDK by developing pertinent research grant applications.

DETERMINING DIRECTIONS FOR PLANNING

The updating of scientific objectives and their utilization in the research application review process takes place through the systematic steps described below.

- Throughout the year the NIADDK staff uses a variety of mechanisms to gather information on scientific progress and emerging research opportunities relative to NIADDK's stated research goals as program staff regularly monitor progress reports of ongoing research. Assessment conference task

forces and scientific advisory groups are convened in areas of special interest. The latest research findings presented at scientific conferences or published in the scientific literature are reviewed. Special studies explore clinical needs, bringing to bear testimony from prominent clinicians, health administrators, and consumers. Congressional directives, plans devised by groups such as the three national advisory boards, the advice of voluntary health agencies, and the results of broad-based evaluation studies organized by the Institute (see below in section on evaluation) are all carefully studied and monitored. These data are then used for assessing progress and identifying scientific opportunities.

- The program staffs of the Institute's four program clusters (arthritis, musculoskeletal, and skin diseases; diabetes, endocrinology, and metabolic diseases; digestive diseases and nutrition; kidney, urologic, and blood diseases) review such data, and each cluster within NIADDK submits a revised annual research plan. The plans summarize progress, submit a tentative revision of scientific objectives, and delineate specific new activities that show unusual promise. New objectives and opportunities are ranked by priority, on the basis of their scientific feasibility, expected costs, and expected benefits in terms of improved health care.

- The annual plans submitted by the clusters are then reviewed by experts, including the Office of the Director of NIADDK, the Office of Program Analysis and Scientific Communications, advisory groups, National Advisory Council subcommittees, ad hoc task forces, and individual scientific experts. In many instances their comments result in further refinement of the plans. For instance, reviewers may indicate that certain areas require further study and may suggest the convening of a workshop, an ad hoc task force, or an evaluation study. Objectives may be restated to take into account such contingencies as available manpower, research resources, or the plans and activities of cooperating organizations throughout the Federal Government and the private research community. The comments on the annual plan are then returned to the program staffs of the four clusters so that they can develop a refined research plan submission, should this be advisable.

- Once the plan has been approved by the Institute Director, it is presented to the Director of NIH and to the National Arthritis, Diabetes, and Digestive and Kidney Diseases Advisory Council.

- In addition to being submitted in a document complete with relevant budgetary information, the Institute's plan is discussed formally with the Director of NIH at an annual research plan review session, at which senior staff of the Office of the Director, NIH, and NIADDK participate. The review session provides an opportunity for the Director of the Institute to elaborate further on specific aspects of the plan and to communicate to the Director, NIH, particularly promising developments and issues of high priority with further detailed background information.

- The National Advisory Council participates in Institute planning in two ways: Its subcommittees review the annual research plan of their respective program clusters, making further refinements, and the four subcommittees and the National Advisory Council as a whole also review the recommendations of peer review groups (the NIH "study sections") with regard to the funding of individual research applications. In this process, the senior biomedical research experts and lay members of the Council implement NIADDK policy. Their recommendations on the funding of particular project applications reflect an overall knowledge of NIADDK policy and research goals, data on scientific progress, the recommendations resulting from peer review of the projects' scientific merit, research priorities as reflected in the annual plan, and budgetary requirements imposed by available funds.

- Once the National Advisory Council has delivered its recommendations, the NIADDK staff carries them out, giving recognition to the priority scores assigned by the peer review groups, the Institute's financial obligations for ongoing awards made in previous years, and the amount of funds available for new undertakings.

These formal steps in the planning process can be viewed as direct planning efforts, specifically designed to ensure that NIADDK supports new research projects of the highest scientific and technical merit, with full consideration of recent scientific progress, health care needs, and the availability of funds.

CONTRIBUTIONS BY EXPERT INVESTIGATORS AND PEER REVIEW

In addition to the individuals and groups who implement the planning effort described above, investigators who plan and conduct individual research projects and their peers in the NIH study sections, who are familiar with the investigators' ongoing work and who review the research grant applications, provide a major contribution to the ordering of priorities. The importance of investigator-initiated research to the Institute is evidenced by the fact that the largest portion of NIADDK's extramural budget is devoted to investigator-initiated research project grants.

Initial action is taken by an investigator who perceives the need for a particular type of research to advance the state of knowledge in his or her field and who then submits a research grant application for a project to be funded by NIADDK. Because the Institute cannot provide funds to every investigator who applies, each application is scrutinized under an exacting review process that involves acknowledged experts in biomedical research, as well as informed laymen.

Incoming grant applications from outside scientists concentrating in a specific field of research are assigned to relevant initial peer review groups (called "study sections") for a rigorous evaluation of their scientific merit and feasibility. A study section composed of experts in the field relevant to a given application will then approve the application in principle or disapprove it. Approved applications are given priority ratings that reflect the study sections' professional judgment of their scientific merit and feasibility.

At the second level of review, the National Advisory Council convenes to review the study sections' recommendations and to make its own final recommendations on whether to fund individual applications. The Council, in its deliberations, looks not only at the scientific merit and feasibility of the proposed research, but also at its value relative to the Institute's program priorities. In this way, varying perspectives help to ensure that the research being conducted under NIADDK sponsorship is necessary work, that it is being performed by qualified individuals, and that it is likely to constitute a worthwhile contribution to the Institute's overall program progress.

Contracts for research are likewise subject to an exacting peer review process. The Institute's requests for research contract proposals (which are published in the broadly disseminated NIH "Guide for Grants and Contracts" and the **Commerce Business Daily** of the Department of Commerce) require a prior formal research concept clearance and development of a project plan, and the resulting applications require scientific peer review and a competitive selection process.

A technical review group composed of experts in relevant fields evaluates all research contract proposals and makes recommendations, ranking the competitors on scientific and technical merit. Finally, contract negotiations are held with the highest ranking competitors, and a final award is made on the basis of both technical recommendations and financial considerations.

Intramural research plans are developed internally but are reviewed by NIADDK's Board of Scientific Counselors, which is composed of acknowledged leaders in basic and clinical medical sciences. This group provides expert advice to the Institute leadership, assesses research progress, and evaluates the productivity and performance of staff scientists.

Thus the full range of NIADDK research programs and funding mechanisms is heavily influenced by expert scientists, either as individuals or in groups. These experts generate new research concepts and proposals, participate in the peer review of project proposals, and advise in the competitive selection of the projects that are scientifically most meritorious.

EVALUATION

Evaluation studies of NIADDK programs have been conducted periodically throughout the Institute's history to provide a rational and informed basis for managerial decisionmaking, provide the Congress and DHHS with mandated evaluation reports, and respond to public concerns for accountability in government. At first, these evaluations were carried out through the Institute's own initiative because it perceived a need for such studies; in more recent years, NIADDK's evaluation activities are pursued under authority of Section 513 of the Public Health Service Act, which mandates the setting aside of 1 percent of all appropriations made under the act for purposes of program evaluation.

Evaluation studies have been undertaken to determine the extent of scientific progress toward the objectives of existing programs. From this assessment, it is determined whether the program has been responsive to perceived needs and whether a change in activities is necessary. The results of the evaluations also provide management with an effective tool to use in maintaining balance between programs and mechanisms of funding. The evaluation process is closely linked with long-term strategic planning as well as with the annual processes of legislative planning and implementation and budget allocations.

In carrying out its evaluation responsibilities, the Institute has often commissioned groups of acknowledged experts in one or more of the diverse biomedical disciplines to make a broad study of a particular area. Using committees of experts on individual aspects of the general subject, these studies have usually required 1 to 2 years for completion. These studies have established the current state of the art, assessed the contribution of the Institute's programs to the field, pointed out the most promising scientific opportunities and new departures for future research, and specified particular needs to be met in order to assure future research progress.

Results of these studies, in the form of detailed reports and study summaries, have been widely disseminated throughout the scientific community, as well as to the Congress and other interested parties. These evaluation studies provide the Institute with an assessment of the effectiveness of its support of research in a particular area, provide the scientific community with future directions for research efforts, and have a direct influence on administrative decisions concerning program structure. As well, they can serve to provide the Congress and concerned private organizations with the data and information necessary for making judgments about future resource allocations.

The Institute has also benefited greatly from planning and evaluation activities conducted by commissions and advisory boards established by the Congress and funded by the Institute. The national commissions on arthritis, diabetes, and digestive diseases also conducted thorough evaluations of NIADDK program activities while developing comprehensive national plans for combating these diseases. Recommendations contained in the respective reports have provided a valuable framework for strategic Institute planning and policy decisions concerning new initiatives.

The following are some of NIADDK's most recent evaluation efforts, the results of which are providing impetus for future Institute direction:

- A recently completed evaluation of research needs in nephrology and urology resulted in publication of a five-volume report, **Research Needs in Nephrology and Urology,** DHEW Publication No. (NIH) 78-1481, that has already had an impact and is expected to continue to serve as a basis for designing future program activity, as a guide to constructing research budgets, and for informing the general public about the needs for research in this area. The evaluation study was accomplished by a series of specialty committees of experts who reported to a coordinating committee. Needs for intensified efforts were recommended in specific areas of basic and clinical research, research resource development, research training, and program coordination.

- A similarly constructed evaluation in the area of cystic fibrosis resulted in the publication of a major report to Congress: **Cystic Fibrosis—State of the Art and Directions for Future Research Efforts,** DHEW Publication No. (NIH) 78-1642. It has been and continues to be a valuable basis for the structuring of current and future NIADDK and NIH efforts in this field.

- A comprehensive evaluation of the needs and priorities of research in skin diseases was commissioned by NIADDK in response to a Senate mandate (94th Congress, Senate Report No. 94-997, p. 52). The final report of this analysis was published as a supplement to the November 1979 issue of the **Journal of Investigative Dermatology,** and has been broadly disseminated. Since the publication of this report, the number of applications with high priority scores for research support in the area of skin diseases has increased significantly. NIADDK is currently drafting program announcements that will invite submission of new project proposals dealing with the various research opportunities outlined in this report.

- Another Senate-mandated study, the evaluation of research needs in endocrinology and metabolic diseases, has been completed, and a comprehensive report was delivered to the Congress in December 1979. Detailed reports of the numerous committees of experts that conducted this evaluation study have also recently been published and will be disseminated broadly. As in the case of all the previously mentioned evaluation studies, NIADDK will take positive steps to implement, within the limits of its resources, the recommendations resulting from this effort.

- An evaluation of NIADDK's hematology program in relation to identification of research needs will be completed in 1981. This project was initiated to analyze the current state of research in hematology, identify gap areas and the technological advances needed to close them, assess the need for a detailed study of hematology research manpower, and evaluate the extramural hematology program of NIADDK in relation to the identified needs.

- The goals, performance, and managerial approaches of the musculoskeletal diseases program will be evaluated in 1981-1982 to provide a foundation for improving research efforts. This project will also provide an assessment of the health care impact of selected medical technologies that have been developed with program resources.

SEVEN

FACTS AND FIGURES

FACTS AND FIGURES

Over its 30-year history, as its research responsibilities have increased, NIADDK's fiscal obligations have also grown (figure 5). Though the Institute's budget has grown to $369.5 million in fiscal year 1981, figure 6 shows that this corresponds to only $184.8 million when adjusted for inflation and expressed in terms of constant 1972 dollars. Resources that were available in the past have enabled the Institute to foster significant progress in many areas. On the other hand, the erosion of available resources by continuing economic inflation

Figure 5.—NIADDK actual obligations, 1951–1981

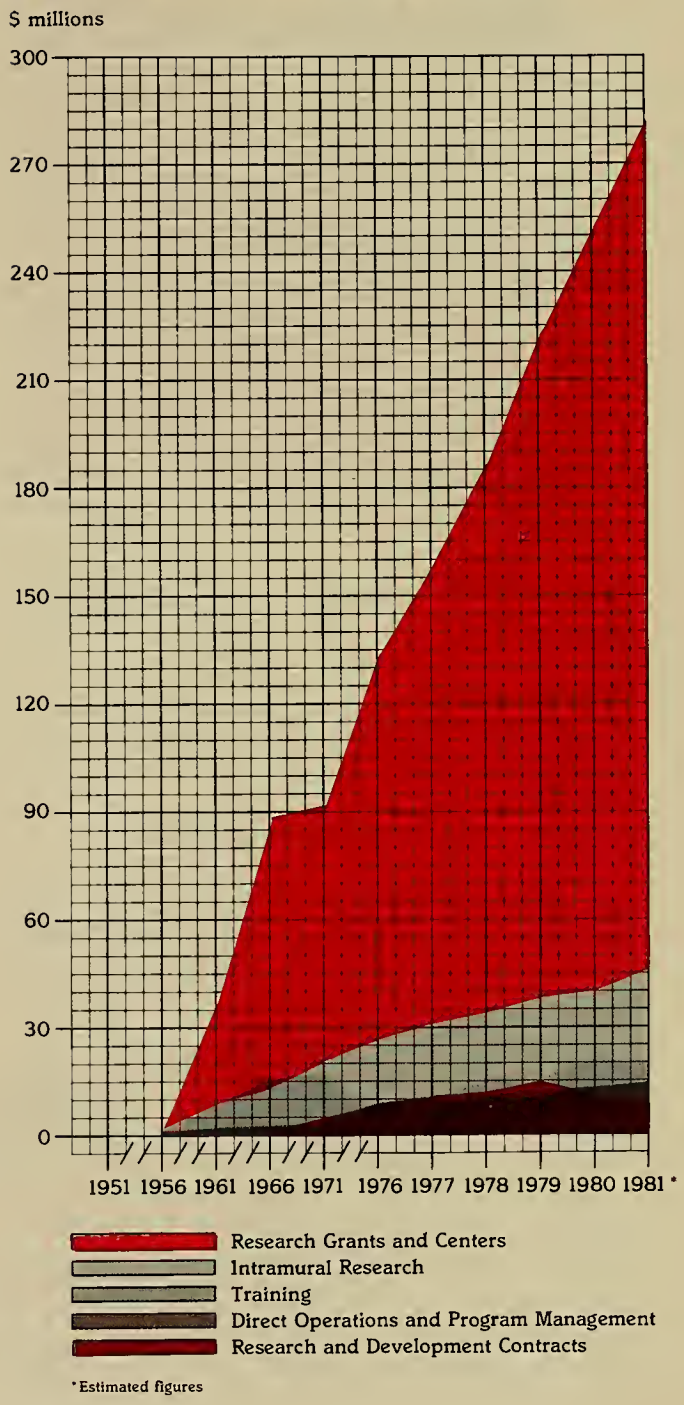
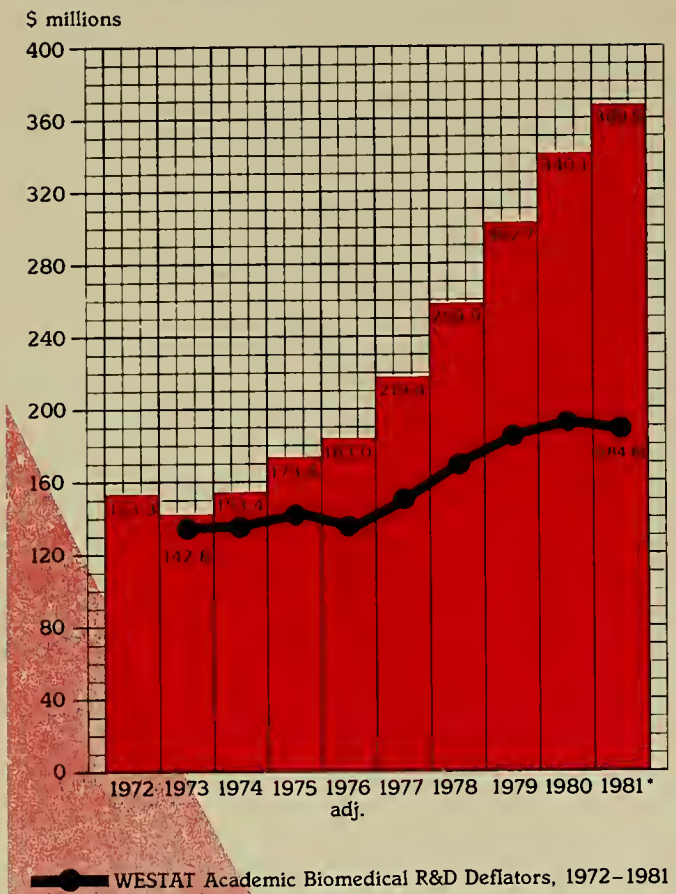


Figure 6.—NIADDK obligations, 1972–1981, adjusted for rate of inflation



underlies the challenge of setting priorities and allocating resources to capitalize on the exciting research opportunities that lie ahead.

RESOURCE ALLOCATION

In the three decades since NIADDK's establishment, rapid expansion and numerous technological advances in biomedical research have brought health and health care to the forefront of domestic policy issues. The inventiveness and ingenuity of biomedical researchers are seemingly limitless; unfortunately, the resources needed in order to profit from them are not. Allocating limited resources is a particularly acute problem within NIADDK. The Institute has leadership responsibility for 10 different, rapidly advancing disease research areas, all of which are of major importance to the Nation's health and, consequently, to its health care expenditures. In light of limited resources, difficult choices must be made in allocations of funding among important programs. These choices are made after much careful planning and in consideration of public health needs and research opportunities to provide appropriate balance and emphasis among high-priority areas.

Table 3 shows the balance of funding allocations among NIADDK's four major program areas and among its 10 categorical programs over the past 10 years.

In carrying out its mission, NIADDK allocates available funding to support research and research training projects in over 400 universities, private and public research facilities, and hospital-based research centers throughout the Nation and in other countries. In addition, the Institute conducts basic and clinical investigations in its intramural facilities at NIH in Bethesda, Maryland, and at field stations in and near Phoenix, Arizona. The Institute's total estimated obligations for fiscal year 1981 are shown in figure 7 by award mechanism, and the geographic distribution of actual obligations for fiscal year 1980 (the latest year for which this information is available) is shown in figure 8.

By far, the greatest portion of NIADDK's budget is devoted to the support of investigator-initiated research grants. Research grant applications submitted by extramural investigators are subject to peer review for scientific merit and compete with other applications in the

Figure 7.—NIADDK total obligations by award mechanism, 1981* (dollars in millions)

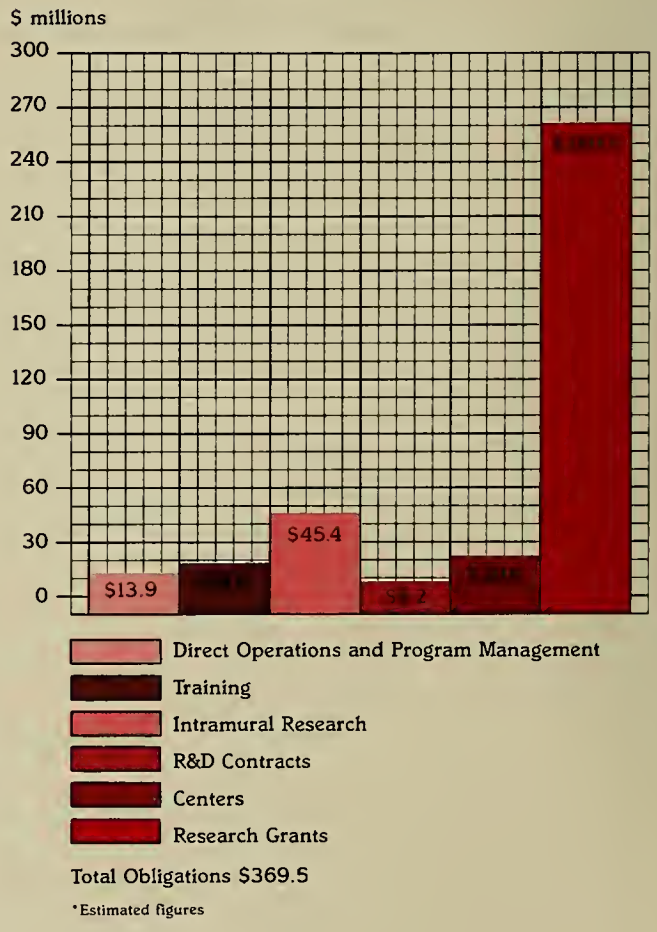
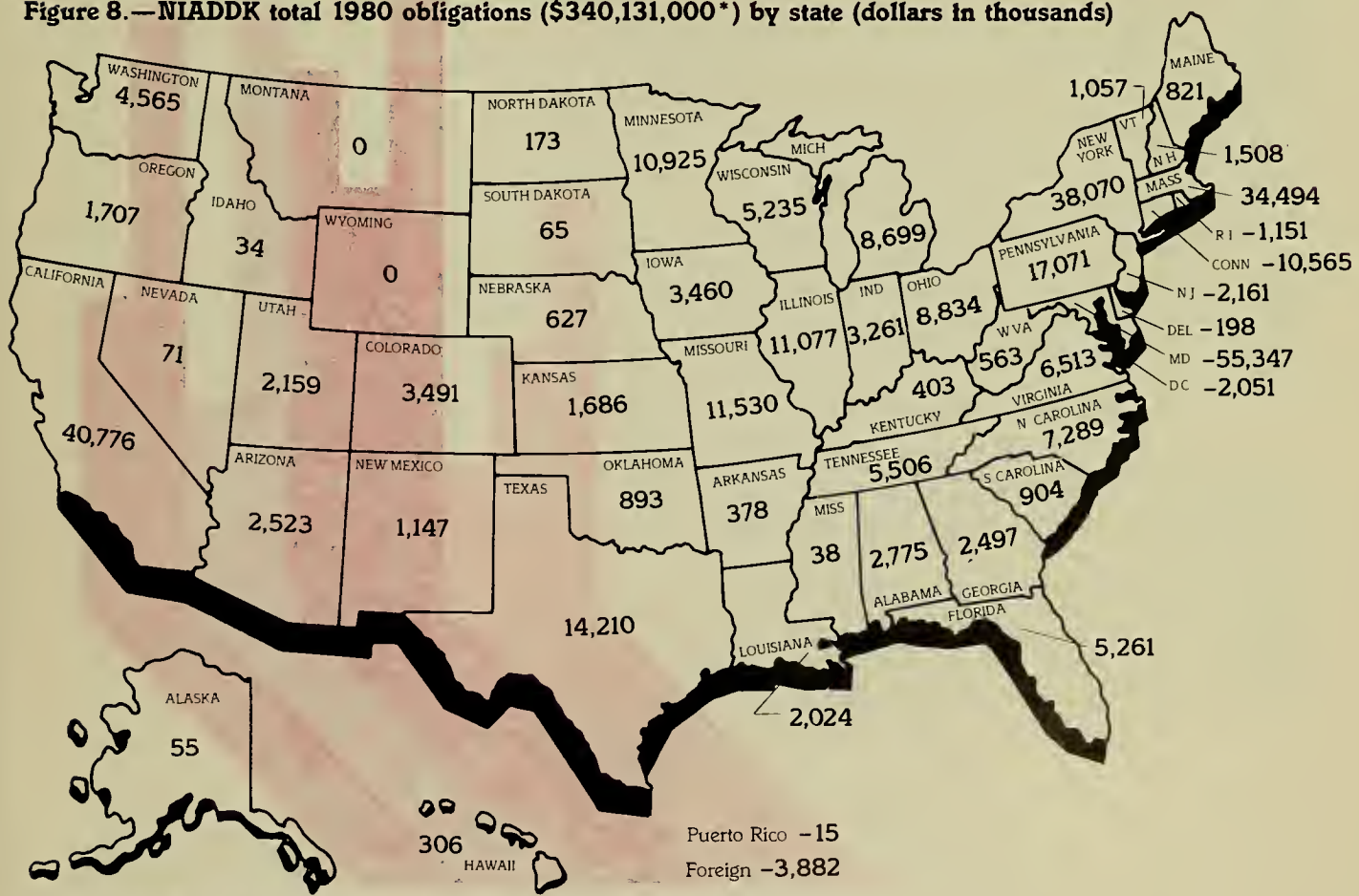


Table 3.—NIADDK program funding, 1972–1981 (dollars in millions)

		1972	1973	1974	1975	1976 adj.	1977	1978	1979	1980	1981*
Arthritis, Musculoskeletal, and Skin Diseases	Arthritis and Related Disorders	$ 14.4	$ 13.8	$ 14.1	$ 16.9	$ 19.1	$ 23.3	$ 27.9	$ 33.8	$ 37.4	$ 43.1
	Musculoskeletal Diseases	5.8	5.6	6.0	7.6	8.2	9.4	10.5	12.6	14.7	16.4
	Skin Diseases	4.9	4.7	5.0	4.8	4.8	6.1	7.5	8.8	9.1	10.1
	**	25.1	24.1	25.1	29.2	32.1	38.8	45.9	55.2	61.2	69.6
Diabetes, Endocrinology, and Metabolic Diseases	Diabetes	8.2	8.2	11.1	14.4	15.4	36.2	53.0	61.1	68.6	72.2
	Endocrinology	19.6	19.0	21.8	23.8	24.3	25.1	27.5	31.8	35.6	37.1
	Metabolic Diseases	32.4	30.6	30.7	32.2	34.0	35.0	37.2	42.1	50.5	54.3
	**	60.1	57.8	63.6	70.5	73.7	96.4	117.7	135.0	154.7	163.6
Digestive Diseases and Nutrition	Digestive Diseases	16.4	16.2	19.9	24.1	25.9	27.7	32.1	36.8	40.5	44.0
	Nutrition	7.9	7.9	8.6	9.6	10.1	10.4	11.6	13.9	15.5	15.9
	**	24.3	24.1	28.5	33.7	36.0	38.1	43.7	50.8	56.0	59.9
Kidney, Urologic, and Blood Diseases	Kidney and Urologic Diseases	18.1	17.7	18.9	21.1	21.1	25.1	26.9	32.2	35.6	40.3
	Blood Diseases	12.0	11.1	11.8	12.5	12.2	12.7	15.2	18.1	19.8	22.2
	**	30.1	28.8	30.7	33.6	33.3	37.7	42.1	50.3	55.3	62.6
All Programs	**	$139.6	$134.9	$147.9	$167.0	$175.0	$211.0	$249.4	$291.2	$327.2	$355.6

*Estimated figures
**Totals may be inexact due to rounding

Figure 8.—NIADDK total 1980 obligations ($340,131,000*) by state (dollars in thousands)



*Includes research grants and centers, intramural research (Arizona and Maryland), training, research and development contracts, and direct operations and program management based on 1980 figures.

same area for available current-year funds. On the average, research grant awards are made for 3 years, and when current-year awards are combined with those awards made in prior years (continuing as a result of a commitment for future support), the Institute has supported about 2,550 individual research projects in 1981. The distribution of these research grant obligations among disease categories in 1981 is shown in figure 9.

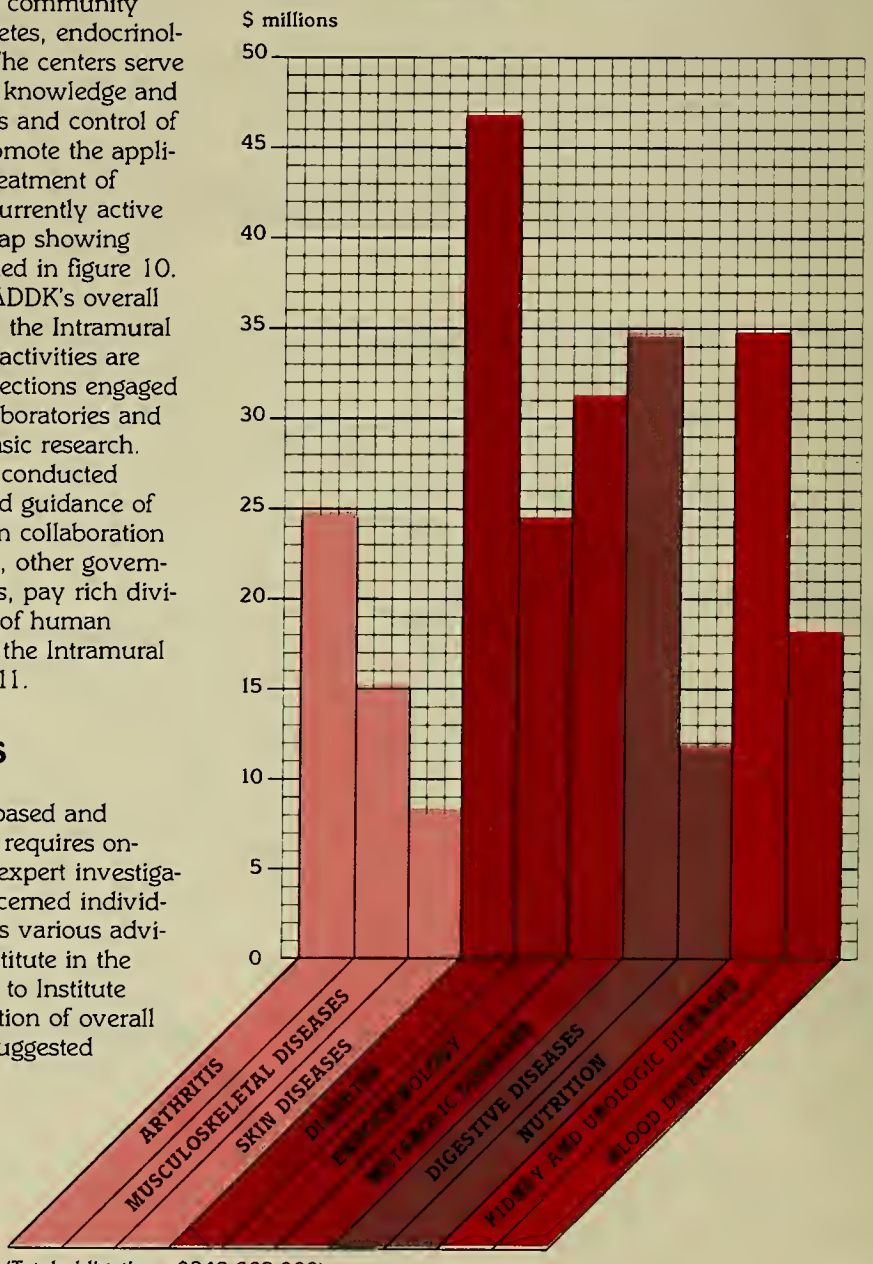
A significant portion of NIADDK's extramural research activity involves the "centers" programs. Through the centers programs, many of which were specifically authorized by legislation in the mid-1970s, 40 institutions are currently designated to foster multidisciplinary approaches to basic and clinical research, patient and professional education, and community demonstration projects in arthritis, diabetes, endocrinology, digestive diseases, and nutrition. The centers serve as a major resource for generating new knowledge and disseminating information on the causes and control of these diseases and demonstrate and promote the application of available knowledge for the treatment of patients affected by them. A listing of currently active centers supported by NIADDK and a map showing their geographic distribution are presented in figure 10.

Another important component of NIADDK's overall research activities and responsibilities is the Intramural Research Program. Intramural research activities are organized into 9 branches and related sections engaged primarily in clinical research, and 10 laboratories and related sections engaged primarily in basic research. The nearly 300 research projects being conducted under this program, with the advice and guidance of the Board of Scientific Counselors and in collaboration with scientists from other NIH Institutes, other government agencies, and outside investigators, pay rich dividends by extending our understanding of human health and disease. The organization of the Intramural Research Program is depicted in figure 11.

ADVISORY GROUPS

Planning and implementing a broad-based and diverse program of biomedical research requires ongoing guidance and contributions from expert investigators, administrators, educators, and concerned individuals from the lay community. NIADDK's various advisory groups provide guidance to the Institute in the form of advice and counsel with regard to Institute goals and programs, review and evaluation of overall program administrative activities, and suggested changes in program structure and operations when necessary. Advisory groups perform an invaluable service by assuring that NIADDK's programs remain responsive to public needs, and they are an essential adjunct to the Institute. The rosters on page 111 detail the current membership of NIADDK's National Advisory Council and Board of Scientific Counselors. As of the end of FY 1981, members of the other NIADDK advisory groups had not yet been designated.

Figure 9.—NIADDK research grant obligations by disease category, 1981*



(Total obligations $248,668,000)

*Estimated figures

Figure 10.—NIADDK centers program

◆ Multipurpose Arthritis Centers

University of Alabama School of Medicine, Birmingham, AL
University of Arizona College of Medicine, Tucson, AZ
University of California School of Medicine, San Francisco, CA
Stanford University School of Medicine, Stanford, CA
University of Colorado Health Sciences Center, Denver, CO
University of Connecticut School of Medicine, Farmington, CT
Arthritis Center of Hawaii, Honolulu, HI
Indiana University School of Medicine, Indianapolis, IN
Johns Hopkins School of Medicine, Baltimore, MD
Boston University School of Medicine, Boston, MA
Robert B. Brigham Hospital, Boston, MA
University of Michigan Medical School, Ann Arbor, MI
University of Missouri Medical Center, Columbia, MO
Washington University School of Medicine, St. Louis, MO
Dartmouth Medical School, Department of Medicine, Hanover, NH
State University of New York, Downstate Medical Center, Brooklyn, NY
Cornell University Medical College, New York, NY
University of Cincinnati Medical Center, Cincinnati, OH
Case Western Reserve University, Cleveland, OH
Vanderbilt University Medical Center, Nashville, TN
Medical College of Wisconsin, Milwaukee, WI

▲ Diabetes Research and Training Centers

Albert Einstein College of Medicine, New York, NY
Indiana University, Indianapolis, IN
University of Michigan, Ann Arbor, MI
Washington University, St. Louis, MO
University of Chicago, Chicago, IL
Vanderbilt University, Nashville, TN
University of Virginia, Charlottesville, VA

△ Diabetes-Endocrinology Research Centers

University of Pennsylvania, Philadelphia, PA
University of Washington, Seattle, WA
University of Iowa, Iowa City, IA

◇ Other Specialized Centers

Peptic Ulcer Center–
University of California, Los Angeles, CA

Liver Center–
University of California, San Francisco, CA

Hepatitis-Cirrhosis Center–
Albert Einstein College of Medicine, New York, NY

Obesity Center–
St. Luke's Hospital Center, New York, NY

Clinical Nutrition Research Units–
Columbia University, New York, NY
Georgia Medical College, Augusta, GA
University of Chicago, Chicago, IL
University of Wisconsin, Madison, WI
Vanderbilt University, Nashville, TN

NATIONAL INSTITUTE OF ARTHRITIS, DIABETES, & DIGESTIVE & KIDNEY DISEASES

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